THE VOICE OF THE PATIENT:

LIVING WITH POLYGLUTAMINE SPINOCEREBELLAR ATAXIAS (SCA) AND DENTATORUBAL - PALLIDOLUYSIAN ATROPHY (DRPLA)

Report of an Externally-Led Patient Focused Drug Development Meeting

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National Ataxia Foundation
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CURE DRPLA

The Voice of the Patient:
Living with Polyglutamine Spinocerebellar Ataxias (SCA) and Dentatorubal-Pallidoluysian Atrophy (DRPLA)
Meeting date: September 25, 2020
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The Voice of the Patient report was prepared by the National Ataxia Foundation (NAF) and CureDRPLA as a summary of the input shared by patients living with polyglutamine Spinocerebellar Ataxias (SCA 1, 2, 3, 6, 7, 8, 17) and Dentatorubal-Pallidoluysian Atrophy (DRPLA) during an Externally-Led Patient Focused Drug Development Meeting (EL-PFDD). This meeting was hosted virtually on September 25, 2020.

This report represents perspectives shared by the individuals who participated in the September 25th meeting and any associated pre-meeting and post-meeting engagement activities. Participant input has been summarized by the authors to represent the comments and themes that emerged from the meeting process. This report does not represent any consensus among participants or the broader population of those living with the polyglutamine spinocerebellar ataxias and does not include all possible perspectives.

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Introduction

The National Ataxia Foundation (NAF) and CureDRPLA facilitated an Externally Led Patient Focused Drug Development (EL-PFDD) meeting on September 25, 2020. This EL-PFDD meeting focused on polyglutamine Spinocerebellar Ataxias (SCAs), specifically: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA17, and dentatorubral-pallidoluysian atrophy (DRPLA). The format of this EL-PFDD meeting was modeled after the work of the U.S. Food and Drug Administration (FDA) Patient-Focused Drug Development (PFDD) initiative. This meeting was held virtually for the health and safety of participants due to the COVID-19 pandemic. The virtual platform allowed increased participation across the United States and the world. Foci of the meeting centered around patient and caregiver perspectives regarding symptoms of the disease and subsequent daily impacts, and perspectives on treatment approaches. The intention of these valuable contributions from caregivers and individuals living with polyglutamine SCAs/DRPLA is to inform the development and regulatory review of new therapeutics for this disease space, which we hope will have a positive impact on the health and quality of life for those living with these diseases.

A full recording of this meeting can be found at: https://ataxia.org/el-pfdd-meeting/

Meeting Overview & Purpose

The National Ataxia Foundation and CureDRPLA conducted a meeting complementary to the FDA's PFDD initiative, to provide various stakeholders the privilege of hearing directly from those affected by polyglutamine Spinocerebellar Ataxias and DRPLA. Topics important to the community and stakeholders were chosen to emphasize the lived experience of individuals and caregivers affected by polyglutamine SCA/DRPLA. Importantly, the participant panels focusing on lived experiences were divided into neuromuscular impacts and other symptoms or health effects. Because polyglutamine SCA/DRPLA cover such an expansive list of symptoms, it was important to distinguish between these two areas. The second half of the meeting focused on current approaches to treatments including what treatments are most important or burdensome which helped to inform the audience of important aspects for a future treatment.

Due to recent innovations in other polyglutamine diseases, such as Huntington's Disease, there is a great deal of pharmaceutical interest and tremendous future potential in treatments for polyglutamine SCA/DRPLA.[1] While these therapies are early in the pipeline, it is important for stakeholders to incorporate the voice of the patient early in the process. The opportunity to hear directly from the patient population will allow better understanding of what patients want in a therapy and what risks and benefits patients will accept and the mode of therapy delivery they will tolerate. On the horizon is gene therapy for the dominant ataxias, and therefore this meeting focused on the polyglutamine SCAs/DRPLA. Testimony from individuals who will eventually be utilizing these therapies is essential so that their lived-experience, needs, and priorities are incorporated into SCA/DRPLA programming, product development, and clinical trial design.

Extensive planning for this EL-PFDD meeting began upon LOI submission in August of 2019. Proposed objectives of the meeting included: (1) To enable SCA/DRPLA-affected individuals to share their perspective on the impact of these diseases on their lives in order to provide the FDA and other stakeholders with a meaningful understanding of the patient experience. (2) To gather and disseminate information regarding SCA/DRPLA-affected individuals and caregivers and their most important priorities regarding potential therapeutic treatment goals. (3) To utilize patient perspectives and goals to

[1] Modified version of Dr. Wilmot's opening remarks

collaborate with the clinical community to gain insights in development of optimal clinical trial design that promotes potential therapeutic treatments.

To inform development of the agenda and polling questions, several members of the SCA/DRPLA community were consulted via phone and email including individuals living with SCA/DRPLA, caregivers, FDA staff, and medical professionals. These consulting partners helped to shape the poignant discussion questions, agenda topics, and real-time polling questions. Additionally, a public comment submission form was utilized 30 days before and 30 days after the meeting to allow opportunities for as many voices from the community as possible. NAF and CureDRPLA members were informed via email, social media outlets, and support group announcements about this opportunity to share their lived experience. A total of 235 comments were submitted, representing the full span of polyglutamine SCAs/DRPLA. In addition, CureDPRLA translated discussion question responses from Japanese families and caregivers of seven individuals with DRPLA, which were included in the final meeting report content.

Due to disruption caused by the novel COVID-19 pandemic, this meeting was conducted virtually to account for the health and safety of all involved. This virtual format allowed for overall increased participation and broke down geographical and accessibility barriers that those with these diseases too often face. This format promoted interactive conversations and allowed moderators to ask in-depth questions as the conversation unfolded. According to the online registration system, 452 people attended the meeting live on September 25th. Live attendees included individuals living with SCA/DRPLA, caregivers/family members, friends, industry members, representatives from other non-profit organizations, scientists, healthcare providers, and FDA representatives. According to the NAF YouTube statistics, the meeting has been streamed 1,423 times (as of 1/14/2021), with an additional 255 views of the meeting from the CureDRPLA YouTube channel (as of 1/14/2021). According to live polling questions[2], 67.9% of responders are living with SCA/DRPLA vs. 32.6% who are a parent, spouse/partner, or caregiver of an individual living with these diseases. Additional demographic information can be found in Appendix 1.

The meeting opened with a greeting from NAF's and CureDRPLA's executive team followed by informative presentations from experts in the ataxia and advanced therapies space. This was followed by pre-recorded panel sessions with participants who either personally experience or who have family members that experience polyglutamine SCA types 1, 2, 3, 6, 7, 8, 17, or DRPLA. The participants provided their experience with symptoms, impacts on daily life, and worries regarding their diagnosis and journey of living the with disease. Select community members also served on a live panel to elaborate in real-time, based on the discussion questions and polling questions (Appendix 2 and 4). To show the severity of the disease as it progresses, a powerful video narrated and produced by a DRPLA caregiver demonstrated the impact of the disease on a family. The afternoon portion featured a pre-recorded panel of affected individuals and caregivers diagnosed with various SCAs/DRPLA to inform the audience about benefits and drawbacks of current treatment options, considerations for clinical trials, and hopes for future treatments. Additionally, a pre-selected group of live panelists participated in questions related to this topic. A full agenda is referenced in Appendix 5. A list of all panelists can be found in Appendix 6. Throughout the meeting, audience members were encouraged to write in with comments or call-in to speak live. All polyglutamine SCAs and DRPLA were represented via panelists, phone calls, and written comments. Participant comments were slightly edited for clarity.

[2] The response rate data for the polling questions are not considered scientific data but provide a snapshot of who participated in the EL-PFDD meeting and are meant to complement the live and pre-recorded comments throughout the meeting.

The National Ataxia Foundation and CureDRPLA anticipate that this voice of the patient report will be utilized by the many stakeholders in the polyglutamine SCA/DRPLA disease community including governmental agencies, regulatory agencies, medical product developers, researchers, and healthcare professionals. The intention of the report is to spotlight themes that emerged directly from the patients and caregivers in hopes of facilitating development of meaningful treatments for those living with these diseases.

Overview of Polyglutamine Spinocerebellar Ataxias[3,4]

Ataxias represent a collection of more than 100 rare diseases, most of which are genetic, fatal, and currently untreatable. Specifically, Spinocerebellar Ataxias (SCAs) and DRPLA are caused by autosomal dominant genetic defects that lead to impairment of specific nerve fibers carrying messages to and from the brain, resulting in degeneration of the cerebellum. To date, approximately 40 different SCAs have been identified. While the prevalence of the SCAs has been difficult to determine, it is believed that collectively, SCAs affect up to 50,000 persons in the United States. The SCAs are rare, progressive genetic diseases that usually begin in early to mid-adulthood and progress over 10-20 years. All polyglutamine SCAs are dominantly inherited disorders, which means that every generation in a family affected by an SCA has a 50% chance of inheriting the gene.

The September 25, 2020 EL-PFDD meeting focused on the group of dominantly inherited forms of ataxia known as polyglutamine Spinocerebellar Ataxias (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA17) and dentatorubral-pallidoluysian atrophy (DRPLA) which is also a polyglutamine disease characterized by ataxia as a major feature. Dominantly inherited means that those who inherit a single copy of the affected gene will have the disease. A polyglutamine disease means that there is a mutation in the gene resulting in an expansion of a normally repetitive element. This mutation gives instructions for a protein (that is made based on the DNA sequence), and the mutation allows incorporation of a string of glutamine amino acids that is too long. That extra length of the glutamine in the protein ends up distorting the three- dimensional structure of the protein and causing problems.

Affected individuals experience debilitating changes to daily living skills such as progressive clumsiness when walking, incoordination when using their hands, and slurred speech. People living with polyglutamine SCAs are often wheelchair-bound within 10 years of symptom onset and may have profound neurological disability beyond ataxia including parkinsonism or other movement disorders, oculomotor disturbance, neuropathy, and spasticity. Swallowing difficulties may lead to the difficult decision to implant a feeding tube for the patient to receive adequate nourishment. Patients' careers or capacity to be employed often end prematurely because of the disabilities caused by the disease. Most of the polyglutamine SCAs are life-shortening with the cause of death often aspiration pneumonia.

The spectrum of age of onset and symptoms varies depending on the type of SCA. When the onset of symptoms is before age 20, the severity of symptoms and the rate of progression increases. In cases of very early onset (before the age of 13), the disease tends to be more severe and progresses much more rapidly. The first symptoms are usually trouble with balance when walking and incoordination of the hands.

[3] "What is Ataxia?" 5th Edition (2017). Matthew Bower, M.S. and Khalaf Bushara, M.D.

[4] Modified version of Dr. Wilmot's opening remarks

While most of the polyglutamine SCAs display an onset in adulthood, because of genetic anticipation, SCA2 and SCA7 symptoms become apparent at an earlier age with each generation. These SCAs have a severe impact on children with early mortality. For those diagnosed in infancy, life span is devastatingly short, often under 32 months.

A short review of each polyglutamine SCA is below. These descriptions are not meant to be all inclusive as the symptoms and the experiences of each person with these diseases varies greatly.

SCA1: As SCA1 progresses over a period of several years, difficulty swallowing and slurred speech are common. In some cases, individuals develop additional symptoms such as neuropathy, spasticity, weakness, eye movement disorders, or memory problems.

SCA2: In addition to incoordination, early symptoms of SCA2 often include neuropathy (loss of feeling and reflexes) and very slow eye movements. Other symptoms might include spasticity, weakness, memory troubles, progressive encephalopathy with autonomic dysfunction, retinitis pigmentosa, and infantile spasms.

SCA3: Impaired balance is usually the first symptom of SCA3, followed later by incoordination of the hands and slurring of speech. Some individuals with SCA3 will notice double vision, and limitation of eye movements, abnormally slow eye movements, or a "staring" appearance of the eyes. As the disease progresses, it is common to experience spasticity, rigidity, loss of muscle bulk and strength, and slowness of movement. In general, SCA3 symptoms tend to be more wide-ranging than those in many other forms of spinocerebellar ataxia. SCA3 is also known as Machado-Joseph Disease.

SCA6: In most cases, the first symptoms of SCA6 are unsteady gait, stumbling, and imbalance. In about 10 percent of the cases, the first symptom is unclear speech (dysarthria). As the disease progresses, incoordination of both upper and lower limbs, tremors, and slurred speech will eventually be present in everyone with SCA6. Double vision or other visual disturbances occur in about 50 percent of the people with SCA6. In later stages, difficulty swallowing (dysphagia) is common.

SCA7: SCA7 differs from most other forms of spinocerebellar ataxia in that visual problems occur in addition to poor coordination. When the disease manifests itself before age 40, visual problems, rather than poor coordination, are typically the earliest signs of disease. In addition, wide-based gait, slow eye movements, and mild changes in sensation or reflexes may be detectable. Loss of motor control and dysarthria become prominent as the disease progresses.

SCA8: Although also caused by a repeat expansion, SCA8 can demonstrate reduced penetrance. This means that while the inheritance pattern is autosomal dominant, not all people who inherit the abnormal SCA8 gene will develop the condition. Typical symptoms tend to manifest in poor coordination, especially of the lower limbs. Other symptoms may include, but are not limited to, difficulty with speech and gait.

SCA17: Spinocerebellar ataxia type 17 (SCA17) is characterized by ataxia, dementia, and involuntary movements, including chorea and dystonia. Psychiatric symptoms, pyramidal signs, and rigidity are common. The age of onset ranges from three to 55 years.

Overview of Dentatorubral-Pallidoluysian Atrophy (DRPLA)[5]

DRPLA is a progressive and aggressive form of polyglutamine ataxia which shares many characteristics with the spinocerebellar ataxias described above. For this reason, the polyglutamine SCAs and DRPLA are grouped together unless otherwise indicated. DRPLA is a rare autosomal dominant genetic disease which is also caused by the expansion of a polyglutamine repeat. In the case of DRPLA, the polyglutamine repeat occurs in the Atrophin-1 (*ATN1*) gene, leading to a distortion in the structure and the function of the ATN1 protein. As the ATN1 gene is expressed in the central nervous system including the cerebellum and in other regions throughout the body, neuronal impairment can be widespread. Symptoms affect most systems in the body and can profoundly interfere with walking, speaking, swallowing, cognition and eventually impact all activities of daily living.

The DRPLA age of onset ranges from infancy to 72 years old with 31.5 years the average. DRPLA is present in the highest rate in people with Japanese ancestry, between 2-7 people per million. Due to the very rare nature of this disease, the incidence of DRPLA in the USA is not yet determined. As with the polyglutamine SCAs, DRPLA manifestations are different for each individual and are progressive, worsening over time.

DRPLA has both juvenile and adult-onset forms of the disease which vary in their presenting symptoms and severity. For adults, the primary clinical features are poor coordination, choreoathetosis, and dementia. Cardinal features in children are progressive intellectual deterioration, behavioral changes, myoclonus, and epilepsy. Maja, a meeting panelist described how "*the progression of the illness of my son who has juvenile-onset DRPLA and my husband who has the midlife DRPLA, is very different. Our son's [disease] is a lot more aggressive*." Maja's quote highlights another DRPLA characteristic: genetic anticipation, which means that a child can start showing symptoms at the same time as a parent, often leaving the non-affected parent as a caregiver to both their spouse and child.

[5] Carroll LS, Massey TH, Wardle M, et al: Dentatorubral-pallidoluysian Atrophy: An Update. Tremor Other Hyperkinet Mov (N Y) 8:577, 2018

Three key SCA/DRPLA themes that emerged from this meeting

This meeting allowed all attendees to better understand both symptoms and the types of treatments that would be meaningful to those affected by the polyglutamine SCAs and DRPLA.

1. **SCA/DRPLA is characterized by progressive deterioration and an intensification of symptoms over time**. Disease characteristics vary greatly between individuals and between the juvenile and adult-onset forms of the disease. Diagnosis can take upwards of five years.

2. **SCA/DRPLA has a heartbreaking prognosis as symptoms eventually become very severe, profoundly impacting the lives of individuals affected as well as their families and caregivers**.
   - In addition to interfering in activities of daily living, the disease impacts all interpersonal relationships. This leads to social isolation and can place an enormous emotional and physical burden on the affected individual, caregivers, and other family members.
   - Caregivers and family members of individuals affected with SCA/DRPLA are forced to live with the fear and anticipatory grief of watching the slow decline of loved ones.

3. **SCA/DRPLA is characterized by a massive unmet treatment need**. There is currently *no curative, disease altering or neuroprotective treatment for the polyglutamine SCAs or DRPLA* and treatments administered to address disease symptoms are not effective. Current treatments including speech/physical/occupational therapy and/or medications are used in an attempt to address symptoms. Many DRPLA representatives commented that there is a lack of knowledge about their disease and potential treatment strategies from within the medical community.

Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients

Symptoms of polyglutamine SCA and DRPLA were divided into two general categories, ensuring that the entire range of symptoms were discussed during the meeting. The first symptom category focused on ataxia and other neuromuscular impacts and the second focused on other important symptoms and health effects. Online polling during the meeting identified and prioritized the top disease symptoms and daily impacts that matter most to patients. An extensive qualitative analysis was conducted of the participants' comments before, during and after the meeting to extrapolate themes that supplement results of the polling data. Each of the polling questions, presentation/discussion comments, and submitted comments were separated by disease type to ensure that there was representation across the disease spectrum and to identify any notable differences in responses by disease subtype. The results of online polling categorized by disease subtype can be found in Appendix 3.

Ataxia and other neuromuscular symptoms

The top three ataxia and other neuromuscular symptoms that matter most to individuals affected by polyglutamine SCA/DRPLA in descending order of priority were: lack of balance, impaired mobility, and decreased coordination and fine motor skills in the hand. These are described below and followed by less common, but still significant neuromuscular symptoms. Again, it is important to note that individuals affected by polyglutamine SCAs and DRPLA experience a wide range of symptoms and the severity of symptoms can vary in different individuals.

Top three neuromuscular symptoms: impaired balance, mobility and coordination

Lack of balance

This symptom received the highest percentage of votes in polling, was mentioned the most frequently in qualitative analysis of the transcript and had the highest frequency of written comments indicating this is a very concerning and debilitating symptom across the polyglutamine SCA types and DRPLA. Several participants commented that balance issues were what first led them to seek medical help leading to an eventual diagnosis. Descriptions involving deteriorating balance often coincided with decreased ability to participate in activities of daily living as described by Destinee, a teenager living with SCA2: *"My balance and coordination are affected so I would leave class early to avoid the crowded halls... [SCA2] affects my balance and coordination making me look drunk while walking and slurring when I talk."* One caller, Shone, a caregiver of an individual living with SCA7 stated: *"My wife retired early from teaching. Her balance issues made it unsafe to be surrounded by preschool age students for their safety in case she should fall."* Destinee recalled an incident when she was a teenager *"on what I thought was going to be a good day, I was at the mall with my friend and we were walking in a candy store. I wasn't using my walker or human support. I ended up losing my balance and falling and screaming. When I fall like that, I don't get a warning just before it happens because my muscles will give out suddenly. Instead of asking if I was okay, customers and workers just glanced with an angry face. A worker came up and asked me to leave in a very rude tone. It's hard for a teenager when good days can easily turn to bad days*" (individual living with SCA2).

Lack of balance was also one of the main health effects and one of the top three most troubling symptoms identified by individuals with DRPLA. Robert, the only panelist with adult onset DRPLA, described it this way, "*I have no balance remaining at all, so dealing with airports [is now] impossible for me."* Many parents of children affected by DRPLA described how they watched their children's "*balance*

deteriorating", how their children experienced "*multiple falls and injuries*", and one described how her child "*increasingly fell down and broke her fingers, nose, and bones."*

Impaired mobility

Many participants spoke of the devastating and debilitating effects of progressively losing the ability to walk and relying on mobility aids as the disease manifests. Chihyang commented: *"As a husband/caregiver with a spouse that has SCA3, I have seen firsthand the aggressive nature of this disease. In the span of 6 years, my wife has gone from running to now requiring assistance with a walker, and soon she will require a wheelchair…We have a beautiful 5 year old that has learned that Mommy's balance is not good, and most of the time, understands that Mommy cannot walk or run the same as other mommies."* The progression of lost mobility over time was especially alarming for those who were affected at a young age. Sherri, a caregiver of two deceased children who experienced SCA7 stated: *"... when he was 14 months, I noticed he wasn't mastering walking. During the next 15 months, we watched Jordan go from walking to crawling to being bedridden. …Sydney seemed to be fine for several years, she began falling at 4-1/2, having gait issues…Sydney would eventually go from walking independently to using a gait trainer to a wheelchair, then being bedridden."*

Decreased coordination and fine motor skills

Ranking third among neuromuscular symptoms, many participants expressed the discouragement they felt as coordination and fine motor skills diminished. Commonly, deterioration of these skills led to significant decline in activities of daily living such as keeping up with school or work and participating in leisure activities. As Cameryn, a young adult with SCA7 stated: *"My coordination and vision became so bad, I had to quit playing the flute. I was devastated."*

Other affected individuals expressed concerns about losing their handwriting skills: *"[My co-workers] said my handwriting was so bad they couldn't read my notes. Well, I knew something must be bad … because I had always had pretty good handwriting …"* (Stephanie, living with SCA6*).* Kerri, the mother of four children affected by DRPLA described how her son: "*is very bright, but he struggles in school because his fine motor skills are so poor. He cannot form legible letters or numbers."* Many of these children require accommodations such as dictation aids or number tiles to help them in school.

Additionally, many spoke about the lack of adaptive tools to assist in combating these symptoms in daily life. As written by Barbara who lives with SCA6: *"…It is getting harder and harder to even prepare a meal because of my balance and lack of coordination. I can't use a manual wheelchair because I have no strength and I can't use an electric wheelchair because of coordination and shaking."* Along with Elaine who deals with SCA6: *"I inherited it from my Dad who had a very bad action or intention tremor in his arms and hands and eventually could not feed himself. That was the symptom that negatively impacted his independence the most and there were no assistive devices or technology to help."* It is important to note that this symptom seemed to be a higher-ranking concern for SCA2,3,6,7, and 17 compared to the other polyglutamine SCAs and DRPLA.

Additional neuromuscular symptoms: muscle stiffness, poor muscle tone/wasting, and neuropathy/numbness/tingling

The following symptoms were less commonly reported than the top three but are still important as indicated by ranking in the polls and themes of the transcript and written comments.

Muscle stiffness (spasticity, rigidity and/or dystonia)

This was one of the top health effects identified by individuals with DRPLA. Naho, whose daughter died from DRPLA-related complications, described how: *"She clutched her hand so tightly that her fingers were crushed nearly to the point of necrosis. The shape of her fingers and nails became deformed. The tension did not leave the hand while she was awake*."

Muscle dystonia tends to be a common feature of SCA8, as illustrated by Lauren, a young adult living with SCA8: *"… a lot of my mobility issues are because of my dystonia and spasticity in my legs; so, I wear bilateral AFOs [Ankle Foot Orthoses] … I have dystonia on the left side of my body. Dystonia is uncontrolled contraction of muscles. This not only complicates the usage of my left arm and leg, it is also painful."*

Poor muscle tone or muscle wasting

Many individuals affected with DRPLA reported poor muscle tone or muscle wasting. Kerri described her son's experience: "*we ended up having to get him a wheelchair with the neck support because he would tire out so quickly when we went places and he had trouble holding up his head. The physical therapist has worked with [him], but because the issue is missing neural connections, it makes it very difficult."* Many parents and caregivers reported that loved ones eventually became bedridden, and many experienced pressure sores and ulcers as a result.

Muscle weakness was mentioned by various individuals with SCA3 in the following descriptions: *"I have lost most of my strength;" "Always tired in my legs;"* and *"…the next thing I knew, I was down on my knees. It was a struggle to get up because the muscles in my legs were weak."* Poor muscle tone was often mentioned despite participants continued dedication to exercise routines, reporting observations like: *"Every day since I was 15, I [have worked] out. But since 29, I keep losing strength" (Brett, SCA1).*

Neuropathy/Numbness and Tingling

Although polling data did not indicate neuropathy as a top concern for individuals living with polyglutamine SCAs, it was mentioned at a relatively high frequency in the qualitative analysis of the emailed comments. A summary of the comments from several people living with SCA 3 or 6, includes descriptions such as *"I had extreme neuropathy in my legs and hands years before any other symptoms occurred"; "neuropathy, especially if it manifests in the hands…[is one of] the biggest challenges with ataxia [SCA]";* and *"Neuropathy in feet and legs—worse when in a reclining position—inhibits sound, uninterrupted sleep at night; makes balance more difficult due to lack of feeling in feet."*

Other symptoms and health effects

A second panel was utilized to review additional symptoms associated with polyglutamine SCAs and DRPLA which do not directly demonstrate motor dysfunction.

Top three other symptoms: dysarthria, cognitive impairment, and dysphagia

Loss of speech (Dysarthria)

Dysarthria is defined as muscle weakness in the face, lips, tongue, and throat that causes difficulty speaking.[6] This symptom was high-ranking across the polling data and qualitative analysis. When polling data was assessed by SCA type, this symptom garnered a high percentage of responses for SCA1, SCA2, SCA3, SCA6, and DRPLA.

[6] https://www.asha.org/public/speech/disorders/dysarthria/ Last Accessed: November 30, 2020.

Speech difficulties are often one of the first DRPLA symptoms to appear. Andrea described how her son with DRPLA "*slurs his words tremendously. I'm one of the few people that can understand him."* Parents noted a deterioration in speech over time as described by Cristi, whose son died of DRPLA-related complications: *"By the age of 13, Reggie began to regress. He was progressively using less words."*

Dysarthria was a common concern for those living with SCA/DRPLA and many mentioned the isolation they feel due to this difficulty with communication. For instance, Tom, an individual living with SCA1 states: *"When speaking, it's hard to form words and sentences…. When my speech is not understood, the speed at which I speak slows down tremendously…. My word retrieval function is slow and continues to [get slower]... The reduction in word finding also makes it hard to pronounce words… Contributing my insight is very hard…I talk so slow that I cannot inject thoughts quickly into conversations… Consequently, I want to withdraw from interactions with others."* Additionally, Jeannette, who lives with SCA3 remarks: *"My slurred speech makes me feel like I have a fat, lazy tongue. Everything sounds great in my head, but it doesn't always come out clear and concise. I still feel self-conscious when going out with friends, I don't speak too often because I am slow and somewhat slurred, especially at the end of the day. I once was an extreme extrovert talking to anyone and to everyone, but this disease has changed my personality to a quiet introvert."*

Cognitive impairment/intellectual disability (inclusive of emotional lability)

Cognitive impairment/intellectual disability was one of the key health effects identified by caregivers and individuals affected by DRPLA. Paul, the father of a teenaged son affected by DRPLA noted: "*Probably … the darkest thing that's happening is the cognitive decline that he is experiencing and the dramatic drop in his IQ over time"*. Cristi described how her late son with DRPLA was "*unable to learn new skills such as his alphabet [and] counting. By age 6, he was re-evaluated, and his IQ had dropped from 86 to 70."* Junko, the caregiver for both her husband and daughter, described the frustration her daughter felt when she "*could no longer read the alphabet she had previously remembered. Kuri repeatedly hit her hands and feet crying, why can't I do that?"* Andrea described her son's experience saying that "*Taeson started kindergarten with an IQ of 90 at a school for children with learning difficulties due to some learning challenges that were identified at age four. He did really well his first year, but the second year he stopped progressing. At that time, we learned that his IQ had dropped to 70. After a few more years of little to no progress, …, we transferred Taeson to a school for children with more severe learning issues, where he remains today. His IQ is now 57."* Paul described the heartbreak of watching his son's decreasing abilities: "*the books that he could read at one time, he can no longer read; puzzles that he could do at one time, he can no longer complete*" (father of son with DRPLA).

Emotional and behavior challenges are prominent with DRPLA. Kerri described how all four of her children with DRPLA "*…have major behavioral issues".* She described how one child "*has to see a psychiatrist for ADHD, oppositional defiance and behaviors on the autistic spectrum. We know the disease can cause psychiatric problems and dementia in DRPLA patients however, the disease is so rare and there's so little research, it is hard to know how much of the kid's behavior is related to the disease."*

This health effect was less commonly reported by individuals with the other polyglutamine SCAs. Cognitive changes were often associated with fatigue especially as the day progressed, as Sherri describes: *"Due to muscle and mental fatigue, he must take a nap during the day to complete the second half of his workday…. The tasks that demand mental sharpness must be done at the beginning of the day"* (caregiver of husband living with SCA7). Tom, a person living with SCA1, discusses the challenges he

notices in emotional lability: *"There are emotional stakes with ataxia [SCA1]. Losing control of my emotions is an ongoing challenge. My reactions can be unpredictable and irrational. Many times I find myself apologizing for something I can't control."*

One woman reported that frustration and DRPLA symptoms such as the loss of emotional control even led to domestic violence. Junko, caring for both her husband and her daughter spoke about how "*the pain of this illness is that even though the families love each other, we can't even live in peace.*"

Swallowing difficulties (Dysphagia)

Caregivers or individuals affected with DRPLA chose dysphagia as one of their top 3 most troublesome symptoms. Often due to issues with neural control or structural issues, dysphagia occurs when weak tongue and/or cheek muscles make it difficult to move food in the oral cavity leading to difficulty masticating. This can lead to the inability to swallow or unsafe swallowing of liquids, foods, or even saliva.[7] As the disease progresses, dysphagia becomes more pronounced and eventually some individuals affected by DRPLA are unable to eat without choking and aspiration becomes a regular activity. Swallowing difficulties may progress so that patients may require a tracheostomy for aspiration and eventually a PEG (percutaneous endoscopic gastrostomy) so that food can bypasses the trachea entirely. The tracheostomy and PEG are options for progressive neurological diseases that affect bulbar function and lead to trouble breathing, inability to eat, or aspiration pneumonia. Family members commented how hospitalizations became more frequent and "*aspiration pneumonia became so common that she couldn't eat through her mouth at all and required gastric valve installation"* (parent of child with DRPLA).

Dysphagia was frequently acknowledged in the written comments and reflections stated during the meeting for all of the diseases. A common theme presented regarding dysphagia was the fear of choking, especially when alone. A plethora of comments surrounding this topic included: *"Swallowing and choking on foods and solids, even saliva, can cause uncontrollable fits of coughing up to 15 minutes in length, leaving me exhausted and scared"* (Tom, SCA1); *"I am embarrassed with choking in public, also concerned with choking when I am alone"* (Jeannette, SCA3); and *"I choke every single day on just water"* (Jodie, SCA2). One panelist emotionally described how they carry a "*barf bag*" with them everywhere just in case their choking leads to vomiting.

Additional symptoms & health effects: fatigue/sleep difficulties, seizures, and visual impairment

The following symptoms were less commonly reported than the top three but are still important as shown by the polls and submitted comments.

Fatigue and/or sleep difficulties

Based on participants' comments, difficulty with sleep often led to increased fatigue for individuals with polyglutamine SCA and caregivers alike. According to the testimony, this fatigue was noticeably more troublesome as the day went on. Laura, the mother and caregiver of a daughter with SCA7 states: *"Maybe, her body is worn out. So yeah, there are good days and bad days, but pretty consistent on starting off well, and by the end of the day, it's a little harder for her."* Participants indicated that increased fatigue led to an exacerbation of other symptoms, as Jessica, whose dad lives with SCA3, articulates: *"And with the sleep, when [my dad] has a bad night, it's awful. The next day is awful. It makes all of his other symptoms much worse."* Lauren with SCA8 stated, "*I find myself needing at least 12 hours of sleep to function normally. So, with school that's been very difficult. And, if for*

[7] https://www.nidcd.nih.gov/health/dysphagia Last Accessed: November 30, 2020

whatever reason, I get less than that amount of sleep, I just find it overall more challenging to control my entire body." Many of the caregivers of individuals with DRPLA also commented on the presence of severe sleep disorders including severe sleep apnea. Sometimes frequent waking is due to myoclonic jerking, which as Kerri described, means that individuals "*rarely sleep more than two to three hours. The doctors prescribed multiple medications to try and help [my son]. He is currently on three different drugs to help him sleep and still only gets four to six hours a night. And even that is not consecutive hours of rest. The lack of sleep makes all the symptoms worse, especially the ataxia."*

Decreased sound sleep for the affected individual, also trended towards decreased sleep for the caregiver as Mary states: *"He is yelling and delusional all night long, I'm five years with only maybe 30 days of uninterrupted sleep"* (caregiver of husband and son who live with SCA2). Kate, a caregiver made a similar statement: "*Also she can't get in deep sleep, she wakes up every hour no matter day or night, we don't think she's able to get a proper rest from it but nothing helps her. As a caregiver, me and my family [are] also having [a] difficult time from this, because this means she needs 24 hours care*" (caregiver of mother with SCA3).

Seizures

Seizures were one of the most severe health effects identified by individuals with DRPLA. Paul described his son's experience: "*the thing that is probably the most alarming [of the] the physical symptoms would absolutely be seizures, where he has grand mal seizures."* With seizures, parents described: **unpredictability**, "*you never know when an epileptic seizure is going to occur";* **intensity**, *"with each seizure comes multiple, prolonged seizure times"*; the **inability to control** and the **progressive nature of seizures**. Cristi described how her son's seizures "*were never controlled and we were on a clear cycle of two good days, often without sleep, and then he would go into a severe cluster of generalized myoclonic and tonic-clonic seizures. He usually had six to twelve seizures in a 24-hour period and did not function at all during that time."* Cristi also has a daughter with DPRLA and described how "*In a 24-hour EEG [electroencephalogram] she would have over 300 generalized myoclonic seizures. It is devastating to watch your child continue to get worse and to watch these seizures."*

Visual impairment (includes weak eye muscles and eye movement disorders)

Broadly, visual impairment encompasses many specific symptoms such as nystagmus (rapid involuntary movement of the eyes), diplopia (double vision), loss of visual acuity/blindness, and other eye movement difficulties. Comments about these visual issues were obtained from individuals with SCA2, 3, 6, 7, 8 & 17. Destinee, a teenager living with SCA2 describes her double vision: *"I get **double vision** when I try to read my phone screen or a book. What happens is all of a sudden, my eyesight gets blurry and my eyeballs start to shake."* Diplopia often correlated with a decrease in leisure activities: *"**Diplopia** initially was partially controlled somewhat with prisms, but ultimately could not correct it. That caused inability to drive, then inability to read or watch TV even. Those losses eliminated much of what she enjoyed in life"* (Ray, caregiver of person with SCA2).

Severe changes in vision also had an impact on participation in daily life, as Laura mentions: *"I think the last time we went to the optometrist, it was steady, but it has definitely been impacted over time for her. So, the past five years she's seen **decline in her vision**"* (caregiver of individual living with SCA7). Echoing this statement, Jason says *"I noticed a major change in my vision, which is a symptom of SCA7. The bifocals I had no longer corrected or improved my vision."* Robert, a University professor with DRPLA, explained his vision challenges: *"The thing, that I lost the most of, for me at least, was the ability to read because…when you work at a university, you read all the time and I can no longer read. I've tried all the magnifying glasses that I can, it still doesn't really help."*

Eye movement disorders, including nystagmus, were also a frequent concern, as Lauren states: *"As a student, **eye movement abnormalities, including nystagmus**, are a large issue for me. Nystagmus makes my eyes have repetitive, uncontrolled movements, which is a great challenge while I am attempting to read for my classes. It takes me more time and more effort than my classmates to complete the same material"* (individual living with SCA8).

Overall impacts of polyglutamine SCAs & DRPLA on daily life

The symptoms of polyglutamine SCAs and DRPLA highlight the subsequent difficulties in Activities of Daily Living (ADLs) experienced by many. Polling data (Appendix 3) indicated the top three concerns were: (1) walking (related to ADL); (2) participating in sports, exercise, or physical activities; and (3) going out, socializing, traveling. Qualitative analysis supported these top impacts on daily life, however the qualitative data also placed significant emphasis on attending school or working and was therefore included in the summary below.

Walking

Walking is usually the preferred method of mobility for ADLs like performing household chores, completing personal hygiene, socializing, attending school/work, exercising, and meal preparation. Of course, modifications can help individuals maintain some level of independence as safe ambulation deteriorates. However, many spoke of their fear of falling, poor balance, and other significant symptoms (such as upper body tremors) as reasons why modifications may not be of benefit. Therefore, difficulty walking was identified as the most significant impact on daily activities indicated by all SCA types and DRPLA.

Michael, an individual living with SCA6 states: *"I am 79 years old and I loved to get out of house but I am wheelchair bound now and it's too hard for my wife (the caregiver). I really have no quality of life because I sit in my lift chair."* Regina echoes: *"Just being able to take a simple step. I'm in my late 40's and I'm insecure of visiting my elderly mother who lives approximately 50 feet away from my home"* (individual living with SCA7). Judy, a caregiver of her son who lives with SCA17 emphasizes how difficulty with walking spills over into challenges in other ADL areas: *"My son is 24 and as a caregiver I need to be with him when he is mobile at all times. He holds on to me sometimes with two arms. Now I am with him in the bathroom and help him with his balance and needs there."*

Individuals affected by DRPLA described their increasing dependence on walking aids, wheelchairs, and other mobility devices as their disease progressed. Robert shared that he could no longer walk around his own home: "*I get around the house, not in a rollator or a walker, but I have a kind of electric cart*" (adult with DRPLA).

Participating in sports, exercise, and physical activities

Exercise is often one of the top recommendations for people living with polyglutamine SCA/DRPLA. However, many expressed the challenges that led to a loss of participation in physical activities. Gina, an individual living with SCA3 states: *"I would love to take walks outside, but I'm afraid of falling with no one to help me. I only have one friend … who I'm comfortable enough with to take walks with and she is not always available…. I would love to go to the gym to exercise. However, I have fallen twice in the gym and I'm afraid I will be too tired for my legs to carry me home."* Stephanie reflects about the loss of enjoyed physical activity: *"And in the next few years, I was no longer playing sports or bowling or doing anything that I normally would do. I was very coordinated. I was a good pitcher, but I no longer had coordination… I was also a pretty good dancer….We used to dance at every New Year's Eve party and weddings, but that was now gone for me"* (individual living with SCA6). Maja, a caregiver for both her husband and son with DRPLA described how the disease has affected her son's

participation: "*With our son, he was attending normal high school, and was attending all the sporting activities, and participating, [and now] he now can't walk without aid. And obviously, he has lost all of those participation abilities, and the social aspect of it. … it's very hard for him to watch his siblings go swimming and go to play whatever sport; and he can't, and he desperately wants to*." Robert, an adult living with DRPLA added: *"I used to be a great runner. The idea that I could even approach doing that now is something that I've lost that I was keen about."* Paul mentioned that *"one of the challenges of having an iPhone with videos of your child is you can see how clearly he could participate in games and speak. And when you see him today, you see a dramatic decline in those abilities*" (father of son with DRPLA).

Attending school/working

Many participants acknowledged how the symptoms of polyglutamine SCA/DRPLA affected their ability to attend school or work. Cameryn eloquently describes how SCA7 affects her educational journey: "*Throughout high school, I felt like I was going to fall over all of the time. I no longer trusted my own legs. I started wearing ankle weights to help ground me. My coordination slowed and I couldn't take notes quickly in class. My voice was changing and people couldn't understand what I was saying. I became frustrated that I had to constantly repeat myself… Now I'm in college and find it hard to take more than two classes at a time. I type slowly, I speak slowly and I need accommodations with taking tests… Someone has to drive me to college and wheel me into class. I haven't had a normal existence since my diagnosis."* Many are no longer able to attend regular classes. Destinee, a high schooler with SCA2 commented: *"Right before Christmas break when walking to my class without human support, my leg muscles suddenly gave you out and I was unable to walk. This forced me to make the decision to finish my senior year online."*

Many participants spoke about how diagnosis and the increasing severity of symptoms forced them into retirement or job loss. Others mentioned how their worries about the progression of symptoms caused them to lose confidence in their work. As Jeannette, an individual living with SCA3 writes: *"I am no longer working… I have a bachelor's degree in business marketing and am an intelligent woman, however my slow and slurred speech make me feel that I do not portray myself as such. Along with my inability to ambulate without assistance, I have completely lost my confidence to go back into the work force."* Eric, living with SCA2 worried about his job performance affecting others. Eric's sister comments: *"He could still do his job and no one else had noticed the symptoms. However, when his unit received orders to go to Iraq, he knew he'd be a liability to himself and others...[after a confirmed diagnosis*]. *He was immediately retired from the army many years before he planned."* Caregivers are similarly affected. Ayaka, the mother of a child with DRPLA reported that her daughter "*requires nursing care for everything and cannot stay at home by herself. The nurses, rehabilitators and counsellors who come to visit have helped me, but I am no longer able to go out to work*."

Going out, socializing, travelling

This key impact on ADL was mentioned by responders representing nearly all the diseases across the polling data and qualitative data. Many emphasized the fear of falling as a significant barrier to leaving their house to travel or socialize. Many made observations such as*: "I can't travel independently for fear that I will not be able to walk even with my cane"* (individual living with SCA3*); "Jason knows if he's not focused when transferring to the bed, shower or car, he will surely fall"* (Sherri, caregiver of husband who lives with SCA7); and *"I can only go out during the day when I can see everything clearly and avoid curbs"* (Jodie, living with SCA2).

Symptoms of SCA/DRPLA inhibit socializing along with worries about judgment of others. An unfortunately common perception from people who are unfamiliar with ataxia, is the misconception that the affected individual is drunk. Gina who lives with SCA3 remarks: *"I lost my balance and crashed into the wall at work. Some laughed and asked me what I had been drinking. That was really embarrassing and hurtful. I'm afraid to have a glass of wine when having dinner with friends because my condition is not familiar to most and I can never pass a sobriety test even if I had nothing to drink."* Brett, who lives with SCA1 states: *"My father had SCA1 and was kicked out of the mall just walking and appearing drunk. Walking to the store, I had the police called on me just [for] walking and appearing drunk. I have been kicked out of 2 bars from bouncers, again just from walking. You look like Frankenstein while walking and people are scared and not for the right reason."*

Other overall impacts on daily life

The polyglutamine SCAs and DRPLA profoundly impact many other aspects of life listed in descending order, including: communication (described in more detail below), performing household tasks or maintenance, driving a motor vehicle or community mobility, personal hygiene and grooming, sexual activity, reading, meal preparation, participating in family or pet care, and other aspects of life. A quote from Robert, illustrated the impact that DRPLA has had on his daily life: "*I can remember when I used to step on the step ladder to change a light bulb in the ceiling. Then I tried that [again] and I couldn't even climb up the step ladder, let alone reach up to the ceiling once I got on top of it. … Most of my later life has been consisting of losing these household duties, one at a time over the last 15 years."* The impacts on daily life can be found in Appendix 3.

Worries about the future identified by participants affected by SCA/DRPLA

Polling responses and qualitative analysis of comments were used to determine the top worries about the future identified by participants affected by SCA/DRPLA. Losing independence and losing the ability to communicate are the top two worries about the future selected by polling respondents. Passing the disease on to the family and disease progression were the top two worries about the future as noted in the qualitative analysis of comments. These four are described in detail and additional worries are listed below.

Losing independence

According to the polling data, losing independence was the highest ranked worry and particularly was noted as a top worry by participants affected by SCA2, 3, 6, 7 & DRPLA. Gina, an individual who lives alone and is diagnosed with SCA3 describes her fear of losing independence: *"I have plenty of family. They are a hundred miles away. They want me to move closer so they can take care of me. I have been a caregiver for my father and I would rather end my life than to have to depend on someone to attend to my every need for feeding, bathing, and other needs."* Michelle is very involved in her brother Eric's life, frequently checking in on his health and safety while he lives alone. She worries about Eric losing independence: *"He is currently living in an apartment by himself, but it can be dangerous. He has had some dangerous falls, including one where he fell into a hot burner on a stove. He has been considering moving to an assisted living at age 46"* (Eric lives with SCA2).

Individuals affected by DRPLA lose their independence as balance, coordination, and cognition decline; eventually requiring assistance for all aspects of daily living. Naho described how her late daughter "*required 24-hour assistance and attendants, and the illness took away her freedom and that of her family*." DRPLA impacts the entire family, as children affected by the disease become increasingly reliant on their parents for all aspects of care. Parents expressed their worry about losing the ability to care for their child at home, either because of the child's condition becoming too severe or because of

the parent becoming sick, injured, or aged. A mother caring for two adult siblings with DRPLA asked "*what should I do when their medical condition progresses, and they become bedridden? Would they be able to continue receiving medical treatment at home?"* Mayuko, a mother of 2 grown children with DRPLA, asked, "*since we live together, what is going to happen if I fall down*?"

Losing the ability to communicate

As individuals affected with DRPLA gradually lose their ability to speak, their family members grieve the loss of communication and connection. Cristi described that after her son's speech regressed, he "*started using an Eye Gaze [communication device] and we knew he was still in there because he could tell us how he felt and what he wanted."* Maja also reported that when it became very difficult for her son affected by DRPLA to speak, he started to use an Eye Gaze, but "*unfortunately because of his epilepsy and myoclonic movements, he can't use that very efficiently."* This made her "*realize how... crucial the ability to speak and communicate is within our societies."* She shared that *"I dread the day when he loses the [ability to communicate] yes and no…it's going to be very, very difficult for him to make any decisions and communicate those decisions."*

Many participants described how the symptoms of dysarthria feel to the affected individual. Further losing the ability to communicate is a worry of many, as Dana summarizes: *"One of the things, that as I progress and go along, the inability to communicate is really scary to me. I know where I am right now. It's sometimes hard to speak clearly and to have others understand me. And I get frustrated at that sometimes. And if I think, down the road a few years, I really shudder to think that communicating is going to be greatly affected and that's, probably, the thing that worries me the most"* (individual living with SCA2).

Passing the disease through the family

The emotional toll of witnessing this disease course through generations of families was stressed over and over throughout this meeting. While holding back tears, Brett who lives with SCA1, states: *"My dad… was very smart and very athletic and I watched ataxia [SCA1] break him."* LeRoy sent in a comment describing the effect of SCA3 on multiple generations: *"Lost my grandma, father, brother, uncle, 1st cousin to this horrible disease. I hope and pray that I don't become that statistic."*

Inherent with this theme is the worry of unknowingly passing the polyglutamine SCA or DRPLA gene to the next generation. While some parents can prevent this through modern In Vitro Fertilization (IVF) techniques, this was not possible many years ago and is not always feasible or the preferred method for today's mothers-to-be. Many comments included themes about fear of passing the affected gene: *"I would never have had children had I known I had late onset SCA6"* (Linda), *"My biggest future worry is about my children and [that] they have [a] 50/50 chance of getting SCA7"* (Sandy), and *"I worry that this disease will affect my boys 31 & 26 and my grandchildren 2 & 1"* (Michael, SCA3).

Due to genetic anticipation, SCA symptoms can become apparent at an earlier age with each generation, depending on SCA type. As Jodie laments: *"And the second real concern is, my grandchildren; [because] SCA2 is hereditary [and] in each generation, the symptoms occur earlier."* This worry was commonly stated throughout the discussions. One mom recants a discussion she has had with her daughter who is affected by SCA7: *"I've had conversations with Cameryn about her future…One of her hopes and dreams is to have children of her own. [Cameryn asks] 'Can I have children? Will I give them this disease?' So just having to have those conversations is heartbreaking, right? She talks about adoption. She has very limited capabilities around the house right now, would she actually be able to care for someone else? So those things, they keep me up at night."*

Genetic anticipation is particularly noticeable in the families affected by DRPLA, where it is common for a parent and a child to be affected with DRPLA at the same time. Maja, Cristi and Junko described their experiences of becoming a caregiver to both their spouse and children with DRPLA, each who had very different needs. With so much of their time devoted to care for the individuals affected with DRPLA, family members and caregivers experience a great emotional and physical burden of their own. Caregivers described how the disease changed their relationships both with friends and with their extended family. Genetic anticipation and the diagnosis of both a child and a parent is also a concern for families with SCA2 and SCA7.

Not knowing how the disease will progress

Participants frequently stated worries related to how, when, and what the disease progression would look like for themselves or their loved ones. Attendees spoke of how SCA/DRPLA feels like *"a downward progression"* and anxiety about *"the possibility of losing the ability to walk, speak, eat and eventually dying"* (Brett, SCA1). Ken who lives with SCA2 worries: *"I have concerns about my ataxia [SCA2]. … just knowing that eventually, it's progressive, and I'll become virtually like a vegetable."* Many participants spoke of the grief associated with losing abilities at a younger age than anticipated: *"Knowing my father's family suffered from Machado-Joseph Disease [SCA3], I had hoped it wouldn't surface until later in life, if at all…I had assumed I'd have already done everything any normal adult would have accomplished in their life and never truly understood the severity of the disease… And unfortunately for me, my condition has progressively worsened"* (Jeannette, SCA3).

For individuals with DRPLA, disease progression is equated with loss. Those affected by DRPLA gradually lose the ability to participate in the activities that they once enjoyed: play, sports, socializing, travel, and reading. They experience social isolation and the deterioration of interpersonal relationships as they can no longer keep up with their friends/peers. Maja reported how her child has "*become very isolated from his peers*" and others even reported bullying by classmates. Paul described the toll that DRPLA had on his son and the heartbreak that he experienced watching the steady decline of a loved one saying "*I get a sense that he has a real sadness and I see him watching his brother do things that he used to do … and you see a real sadness in his eyes that he knows that at one time he could do that. He can't now. I think probably what makes him saddest is he doesn't really understand why he can no longer do it and that's very, very, very sad thing as a parent to watch that."* As DRPLA progression continues, losses become more profound. Andrea described how she lives "*in fear of the future knowing what the DRPLA disease progression looks like."*

Other worries about the future

In addition, participants expressed other worries during the polling responses, discussion, and in emailed comments. These included: having to move into an assisted living or skilled nursing facility; losing the ability to swallow, choking; dying prematurely; becoming a burden to their family; losing mobility and being bedbound; losing the ability to walk unassisted/ becoming dependent on a mobility device; not having the energy to work and live as they want to; not knowing if they can support themselves and/or their family financially; not being able to afford their healthcare; not being able to care for their children; losing friends; perceptions from others such as looking drunk or abnormal; not finding a cure; and requiring hospitalization.

Topic 2: Patient Perspectives on Approaches to Treatments

This topic was meant to reflect individuals' experiences of the current treatment options and to gather information about ideal future treatments and other important considerations. As with the previous topic, real-time polling was used to capture the perspectives of individuals and caregivers of

those affected with SCA/DRPLA (Appendix 2). A qualitative analysis was conducted of the meeting transcript and comments submitted to the public portal and were used to support or refine common themes. The greatest differences between responses from individuals with SCA and individuals with DRPLA were observed in this topic, possibly reflecting the more severe symptomology of DRPLA.

Medical/pharmaceutical treatments only focus on symptom management

Currently, there are no curative or disease modifying therapies for the polyglutamine SCAs and DRPLA. Current treatment approaches can only be used to control or manage disease symptoms and not to treat the disease. The top three types of therapeutics for participants with polyglutamine SCAs were (1) dietary and herbal supplements, (2) prescription medications for muscular issues (Pregabin, Baclofen, Amantadine, Riluzole, Dalfampridine), and (3) over the counter (OTC) pain medications (acetaminophen, ibuprofen).

Eleven percent of participants reported that they did not take any medications, while all DRPLA respondents use pharmaceutical drugs to manage symptoms. (Appendix 3) The top three medications taken by individuals with DRPLA were (1) antiseizure medications (depakene, E Keppra, Mystan, Vimpat); (2) prescription medications for muscular issues; followed by (3) other medications not mentioned in the poll including sleep medications (doxepin, trazodone), medications to treat ADHD (clonidine, Guanfacine, Adderall), and antipsychotics (Risperdal, Abilify).

Comments made during the meeting often described the use of prescription medicines to attempt to treat specific symptoms, often with little effectiveness or debilitating side effects: *"I take Baclofen, eight pills a day, and Chlorzoxazone, four pills a day. They create nausea and dizziness but it's not as bad as ataxia so I'm okay with the side effects. They help with my muscle tightness and spasticity and seem to be relieving the symptoms by about 30%. …I also take arginine, 10 pills a day for repairing cerebellar receptors. I read about that in a study from Japan. I'm not sure if either of them are doing anything but I keep taking them because I'm scared not to. I am 34 and I take over 20 pills a day, just to be a third of the effectiveness of a regular person*" (Brett, SCA1). A few comments indicated some effectiveness of prescriptions targeted at symptoms: *"After I started the Riluzole, I could shave without cutting myself, so that was an accomplishment"* (Doug, SCA6). Although OTC medications were identified in the top 3 approaches per the polling data, they were rarely mentioned in the transcript or comments. Instead, medical marijuana and/or CBD oil was frequently mentioned in the qualitative data, typically for pain management, to increase appetite, and to help with sleep. However, participants spoke about barriers such as cost of re-certification, its negative effect on balance and coordination, and variable effectiveness.

A treatment challenge frequently identified by individuals with DRPLA was that some health care professionals were unfamiliar with the disease. This lack of understanding made parents of children with DRPLA feel dismissed. Kerri described her experiences when seeking therapies for her children: *"I had been told by most doctors that there is nothing that they can do and basically take them home and watch them die, in not so many words. As a condolence, they would say, 'come back when the seizures start and we can treat those, but there's nothing else that we can treat'*." Naho echoed this when describing her family's experience, "*we felt that medical professionals and related services had a poor understanding of disease and symptoms of DRPLA, and a poor knowledge of the best therapy."*

Individuals with polyglutamine SCAs also mentioned unfamiliarity of the disease within the medical field, but to a lesser extent. Instead, there was a greater concern about the lack of treatment, and many relayed their frustration with the ineffectiveness of a patchwork of symptom management. Mark, an individual living with SCA3 describes it this way: *"The real problem is the lack of treatments.*

Sure, we can treat some of the symptoms, but to a very limited extent. If followed with diligence, therapies can restore some functionality for a time, but progression of the disease inevitably means deteriorating function. Drugs aren't any better. There are often significant side effects (not to mention costs). Nothing available actually solves the problem, and it's likely increasing dosages will be required. Also, each symptom requires its own set of therapies and drugs. These can collectively add up to an overwhelming number of medications and therapies to keep up with and can become a problem in and of itself."

Top treatment approaches besides medication: exercise for SCA, physical therapy for DRPLA

According to the polling data, the top non-pharmaceutical treatment approach for SCA is through exercise, followed by use of mobility aids (walkers or wheelchairs), and physical therapy. Additional high-ranking approaches included: a modified home environment, then occupational and speech therapy. Only 2% of the participants who responded to the polling, are *not* currently using any of these approaches. (Appendix 3)

A large portion of the discussion was dedicated to the benefits of exercise. Many described how they believed that exercise helped slow symptom progression and discussed the approaches that they took to feel better and to maintain their function and improve balance, strength, and coordination. Common forms of exercise mentioned included biking, walking, yoga, and swimming. Colin, the caregiver for his wife states: *"My wife, who now uses a wheelchair permanently, has been doing Pilates classes since she was diagnosed some 12 years ago. Whilst this hasn't necessarily prevented the onset of the condition it has definitely contributed to her overall body strength and wellbeing"* (SCA3). Gregory elaborates on his perceived benefits of biking: *"I ride my recumbent trike over an hour a day (15-20 miles). I used to be an avid (bi)cyclist; but can no longer balance. It is extremely tiring; but it seems to slow down the onset of symptoms"* (SCA3).

At the same time, participants spoke about many frustrations associated with exercise. For instance, Hannah, a young woman who lives with SCA1 states: *"I'm definitely not a strong as an athlete, but I try to keep up with 30 to 60 minutes of exercise every day. I truly believe in the positive effect exercise can have. But it feels like exercise is the only treatment I hear about over and over for ataxia [SCA1]."* An additional concern for those living with SCAs is the importance of participating in the right amount of exercise. Too little and the effects go unnoticed, too much and the effects spill over, making other symptoms more difficult to deal with. Jessica, who lives with SCA3 and witnesses her dad's life with SCA3 states: *"His only other treatment is moderate exercise using his recumbent tricycle and swimming. This must be regulated though, as excessive exercise has a negative effect on his sleep, while not enough causes increased ataxia symptoms, such as spasticity, cramping and balance."* Lastly, another frustration indicated was a loss of participation in exercise as disease symptoms progressed. Michelle, the support system for her brother comments: *"To keep this overall strength, Eric has tried to stay active. He works out in a gym. He also rode multiple different tricycles since he couldn't balance on a bicycle. This was great until it became too difficult to use"* (SCA2).

Individuals affected with DRPLA reported using physical therapy above all other therapies and approaches, even exercise. Aqua therapy and special education programs were more frequently reported by people with DRPLA. Individuals with DRPLA reported requiring many other types of therapies and treatments including medical visits to maintain some of their adaptations (cannula replacement every two weeks, PEG replacement every three months, catheters), rehabilitation, dental checkups, music therapy, speech therapy, osteopathy, and swallowing training.

Based on her experience caring for her husband and son, Maja encouraged all those affected with SCA/DRPLA "*to seek any assistance, whether it's physiotherapy, occupational therapy, and try to keep yourself healthy … I would encourage people to keep exercising, keep reading to your children, read the newspapers out loud, try to use the facilities that you have, and the abilities that you have for as long as you possibly can*." While this approach works for many, Andrea reminded everyone that this doesn't work for all and that "*exercise is wonderful but when your child has an IQ of 57 and walking is hard, it is very difficult to get him to exercise*" (mother of child with DRPLA).

Lack of efficacy is the top limitation of current treatment approaches

The biggest treatment challenge for those affected by polyglutamine SCA and DRPLA is the absence of disease modifying or curative therapies; current treatment approaches can only control or manage symptoms. When asked to select the top three major challenges with current treatment approaches, the top response from all participants was that therapies are not very effective (Appendix 2). This lack of efficacy was reflected in the answers to the question about how well their current regimen (both medications and non-medications) control symptoms. 51% of participants affected with SCA responded that their current regimen controls the symptoms somewhat, 29% responded that their treatment controls symptoms very little, while 11% affected with SCA felt that their current regimen is controlling their symptoms to a great extent. Responses were different for individuals affected with DRPLA; most (60%) responded that their current regimen controls their symptoms very little, with the rest split equally (20%) between "somewhat" and "not at all", consistent with comments from family members/caregivers of individuals affected with DRPLA (Appendix 3).

Individuals affected by SCA and DRPLA identified the other top limitations of current therapies as the high cost or lack of insurance coverage, followed very closely by limited availability and negative side effects (Appendix 3). Qualitative analysis indicated these same limitations, along with frequent mention of the difficulty knowing if the treatment is effective and the frustration with finding the right balance of treatments.

Lack of coverage by insurance or high cost was a significant barrier for the use of treatment options for symptom management. For instance, Hannah who lives with SCA1 speaks about barriers to participation in physical therapy: *"Shortly after my diagnosis, my doctor also sent me to physical therapy…. Because ataxia [SCA1] degeneration happens so slowly. I was not showing enough progress for insurance to justify that I continue physical therapy."* Eric and his support system express how many different treatment suggestions they have attempted, such as a balance vest, medical marijuana, and various medications. But the combination got too expensive, forcing their family to make difficult decisions: *"He also tried medical marijuana. His neurologist suggested trying it to see if it would help with any symptoms. It did help him sleep better, which helped with the fatigue. It also helped his lack of appetite... However, the yearly certifications were expensive in addition to the prescriptions. So he made the decision not to continue"* (Michelle, caregiver of brother who lives with SCA1). Many commented about lack of insurance coverage for the SCA/DRPLA disease space even though the medications treat symptoms. As Jessica states: "*Even just looking at my current situation, I just started having really bad restlessness at night in my arms and my legs…Just the prescription that my neurologist wanted to give me, I'm already struggling with insurance, trying to get it approved…I'm going to try to naturally figure it out; do a better sleep pattern and things like that. But it's very discouraging when that happens, the very first symptom I have, I'm struggling to get the medication that I need"* (SCA3). Lauren submitted similar commentary: *"Nystagmus makes my eyes have repetitive, uncontrolled movements, which is a great challenge while I am attempting to read for my classes…While there is a medication that improves this phenomenon, it is not FDA approved for SCA so I must get it compounded and pay out of pocket."*

Negative side effects of medications were identified as a treatment limitation for those affected by polyglutamine SCAs and DRPLA, and this was reflected in many comments made during and after the meeting. Kerri described the impact of side-effects on her daughter affected by DRPLA: "*the medications help the behaviors but make her drowsy during the day and awake all night. Trying to find a balance is a constant struggle because the way she metabolizes the meds changes frequently as the disease progresses and as she grows and changes*." Jackie, the mother of a young adult who lives with SCA17 articulated the very real trade-off that parents are faced with when making medication decisions for their children: "*My daughter, Angela was diagnosed when she was 15, she's 28 now. And she was on one medication to try... just to maybe give her a longer timeframe where she could use a computer and things like that, Carbidopa-Levodopa. And she was so, so sick from it: vomiting and she went down to about 70 pounds. …she had to be weaned off of it because she was on like 12 pills a day…. And so now our daughter, she cannot walk, she cannot speak, she cannot move her arms or move her eyes on command…We could not put her on any medications because she could not communicate to us if she is now in pain or if she's hurting. Because of what she went through before, we just couldn't do that to her."*

Polling responses and comments from caregivers and individuals with DRPLA noted the very high doses of medications administered to manage symptoms. Seizures were a symptom that was reported as being particularly difficult to manage. Many described how the medications had to be periodically increased until their family members were taking the maximal possible dose. Andrea described how her son "*takes 19 pills a day, 16 of which are for seizure control*." Mayuko stated that "*I can't say that her epileptic seizures have been particularly improved by increasing the dose of medication. She has tried almost every kind of medication and I think I'm at the upper end of it, at the maximum dose*."

Another common theme that emerged from the voices of patients during the meeting, was that due to the slow progression of the disease, it is hard to measure whether treatment is helping. As Brian summarizes*: "Well, I think it's really difficult to determine improvement. Because, even if something slows the progression, that's really difficult to measure"* (SCA7). Greg, who lives with SCA2, elaborates: *"I didn't notice anything from the physical therapy….Maybe long term there is some effect, but short term it was hard to notice any effect at all... In the time that it took each day to do the exercises, [it] didn't seem like there was enough improvement to continue."* Kerri has the advantage of cell phone footage to compare progression over time for her DRPLA-affected children: *"My children use medical cannabis oil to treat their symptoms. It has helped my son with his myoclonic jerking. I believe it has slowed the progression. It is very difficult to know how bad it would have been without it, but as I reviewed videos, I had forgot how bad his myoclonus was before he started it".*

Short of a cure, the ideal future treatment will slow or stop disease progression

The most meaningful outcome in a future treatment is the slowing or stopping of disease progression, followed by improvement of coordination and balance. Meeting participants also requested the following from a medication: an improvement in disease symptoms such as speech and walking, regaining strength and or muscle function, lessening of seizures, fatigue, pain, numbness or tingling. Analysis of the transcript and emailed comments produced similar themes, along with the desperation for a viable treatment, excitement about the prospect of gene therapy, and a willingness to participate in clinical trials to move closer to adequate treatment.

Participants with SCA frequently spoke of the hope for a treatment that would halt disease progression. Greg states: *"Since I'm in early progression, stopping progression would be the most important thing to me, where it stops progression where I'm at now, where I can continue to live*

independently like I am" (SCA2). Some participants identified specific areas of the disease where improvement would greatly affect their lives. For instance, Carol who lives with SCA1 comments: *"My desire is for a drug to help with balance. I am not one to take any pharmaceutical drug, not even for my high cholesterol, yet I would take anything, even with high risks, to be able to walk even semi-normally again."* Laddy, an individual living with SCA8, commented about the symptoms she would like a treatment to address: *"Speech - tired of going to a restaurant, ordering, and not being sure if I was understood till I get the order. So speech intelligibility would be huge."*

Family members and caregivers of individuals affected by DRPLA requested the rapid development of a treatment for the disease, especially one that could increase ADLs and help maintain independence. Naho asked for "*Medications that can stop the onset of the disease before it occurs, to slow down the progression of the disease, or alleviate the symptoms.*" Some articulated a wish for medications to specifically "*help improve or restore some of the neural connections or at the very least halt the decline*", and to "*improve the ataxia and myoclonus and preventing the seizures from starting*." Kerri described how "*preserving their independence is essential*". Cristi described how "*of all the symptoms that my daughter has, I just wish that she could take care of herself again. We have to help her get dressed. We have to help her go to the bathroom. I remember when she was completely normal*."

Other important treatment considerations

Treatments need to be suitable for the community they are intended to treat.

A very significant challenge for those affected by DRPLA is how the difficulty in swallowing limits taking the medications. Maja explained how: "*one of the big symptoms of many people with polyglutamine SCA/DRPLA is dysphasia. You are trying to swallow these massive horse-like tablets or supplements that are meant to be good for you, but we tried one and it was 10 massive tablets per day and there was absolutely no way our son could physically do that."* Naho, whose daughter passed away from DRPLA also identified a need for "*medications that are easy to take because of the high frequency of intellectual and cognitive impairment and swallowing problems*".

Due to progression of symptoms and increasing age, many participants indicated that treatments needed to be easily accessible. For instance, Jessica (SCA3) states: "*I have many relatives that also have ataxia [SCA] and one of them does live alone. And I could see if there was a treatment that you had to go somewhere regularly…with ataxia[SCA], that's very challenging. So I can see where that would be very difficult."* Tom (SCA1) elaborates on current difficulties getting to therapy: *"I have a hard time getting to physical therapy and occupational therapy because I can't drive. I do depend on members of my family but it's pretty sporadic as far as getting to things."*

Individuals living with polyglutamine SCAs and DRPLA are willing to participate in clinical trials.

Many participants mentioned that they are currently participating in Natural History Studies or other symptom-management studies. Some expressed frustration with the restrictive inclusion criteria and the seemingly slow progress towards treatment. Many were hopeful that scientists and other necessary parties will continue to strive for progress towards a treatment, such as gene therapy.

Biomarkers and accurate disease measurements are necessary.

As the progression of polyglutamine SCA/DRPLA is so slow, it is sometimes challenging to know whether treatments are beneficial or not. As a result, any treatment needs to be measured in a way that doesn't rely on subjective symptom evaluation, but "*should rely on scientific evidence or improvement within biomarkers or other recordable data*" (Paul, father of son with DRPLA).

Conclusion

Although progression of symptoms and timeline varies between individuals and disease type, these multifaceted diseases produce symptoms that severely affect quality of life. This meeting allowed individuals and caregivers of those living with polyglutamine SCAs and DRPLA to tell the FDA and other stakeholders first-hand what it is like to live with a polyglutamine SCA or DRPLA and the kinds of treatments that would be tolerated and are so necessary for this community. It was well articulated that balance and walking were the biggest symptomatic concerns. The idea of losing independence and diminishing speech capabilities was very worrisome for patients. Throughout this EL-PFDD meeting, individuals with polyglutamine SCA and DRPLA expressed their willingness to support the development of new treatment options, even if treatments may not be approved in time to affect their own course with the disease. Current treatment options simply don't exist, and symptom management is reported to have low effectiveness and high burdens.

While all of the polyglutamine SCAs are debilitating, anticipatory grief was noted frequently among the individuals and families affected by DRPLA. Cristi described how "*the consistent progression of DRPLA is living a slow and painful life of grief, grief of the loss of normal, anticipatory grief of the next loss and ultimately grief in likely death".* Paul summed up the situation: "*what is very clear is if we do not find a cure for this disease, it will kill my son*."

Appendices

Appendix 1: Demographic Polling Responses of Meeting Attendees

1. As it relates to Spinocerebellar Ataxia Type 1, 2, 3, 6, 7, 8, 17, or DRPLA, are you?	Total responses	46	
	Unique participants	46	
	Response options	Count	Percent
	An individual living with one	31	67.39
	A parent, spouse/partner, or caregiver of an individual living with one	15	32.61

2. Where does the affected individual live?	Total responses	59	
	Unique participants	59	
	Response options	Count	Percent
	US: Midwest	18	30.51
	US: Northeast	12	20.34
	US: West	10	16.95
	US: Mid-Atlantic	7	11.86
	Europe or UK	6	10.17
	US: Mountain	3	5.08
	Australia or New Zealand	1	1.69
	Canada	1	1.69
	Other	1	1.69
	Asia	0	0
	Africa	0	0
	Central or South America	0	0
	Japan	0	0

3. What is the affected individual's age?	Total responses	67	
	Unique participants	67	
	Response options	Count	Percent
	50-59 years	19	28.36
	60-69 years	15	22.39
	40-49 years	14	20.9
	18-29 years	5	7.46
	30-39 years	5	7.46
	70-79 years	4	5.97
	Younger than 12	3	4.48
	12-17 years	2	2.99
	80 or older	0	0

4. At what age was the affected individual diagnosed with SCA/DRPLA?	Total responses	70	
	Unique participants	70	
	Response options	Count	Percent
	50-65 years	27	38.57
	31-49 years	25	35.71
	19-30 years	9	12.86
	9-18 years	3	4.29
	3-8 years	2	2.86
	Over 66 years	2	2.86
	Birth to 2 years	1	1.43
	Not sure	1	1.43

Appendix 1 continued

5. After the affected individual started experiencing symptoms, how long before genetic testing confirmed the diagnosis?	Total responses	68	
	Unique participants	68	
	Response options	Count	Percent
	More than 5 years	20	29.41
	1-2 years	14	20.59
	Less than 1 year	13	19.12
	3-5 years	11	16.18
	Not sure	10	14.71

6. What condition has the affected individual been diagnosed with?	Total responses	66	
	Unique participants	66	
	Response options	Count	Percent
	SCA3	19	28.79
	SCA6	15	22.73
	SCA2	8	12.12
	DRPLA	7	10.61
	SCA17	5	7.58
	SCA1	4	6.06
	SCA7	4	6.06
	SCA8	4	6.06

Appendix 2: Cumulative Polling Results for Topics 1 & 2

Topic 1, Q1. Which of the following SCA/DRPLA-related health effects does the affected individual have or had in the past? Select ALL that apply	Total responses	527	
	Unique participants	70	
	Response options	Count	Percent
	Lack of balance	67	12.71
	Impaired mobility	62	11.76
	Speech or swallowing difficulties	55	10.44
	Decreased coordination/fine motor skills in arms or hands	54	10.25
	Muscle stiffness (spasticity, rigidity, dystonia)	48	9.11
	Fatigue or sleep difficulties	42	7.97
	Poor muscle tone or muscle wasting	40	7.59
	Visual impairment (weak eye muscles and eye movement disorders)	38	7.21
	Depression or anxiety	30	5.69
	Numbness and tingling	28	5.31
	Cognitive impairment/intellectual disability	26	4.93
	Uncontrollable limb movement	21	3.98
	Other	11	2.09
	Seizures	5	0.95

Topic1, Q2. Select the most troublesome SCA/DRPLA-related health effects that the affected individual has: Select Top 3	Total responses	211	
	Unique participants	73	
	Response options	Count	Percent
	Lack of balance	54	25.59
	Impaired mobility	42	19.91
	Speech or swallowing difficulties	33	15.64
	Decreased coordination/fine motor skills in arms or hands	21	9.95
	Muscle stiffness (spasticity, rigidity, dystonia)	15	7.11
	Fatigue or sleep difficulties	11	5.21
	Visual impairment (weak eye muscles and eye movement disorders)	11	5.21
	Cognitive impairment/intellectual disability	8	3.79
	Poor muscle tone or muscle wasting	4	1.9
	Seizures	4	1.9
	Other	3	1.42
	Uncontrollable limb movement	2	0.95
	Numbness and tingling	2	0.95
	Depression or anxiety	1	0.47

*The response rate data for the polling questions are not considered scientific data but provide a snapshot of who participated in the ELPFDD meeting and are meant to complement the live and pre-recorded comments throughout the meeting.

Appendix 2 continued

Topic 1, Q3. What specific activities of daily life are most important to you that you are unable or have difficulty doing because of SCA/DRPLA? Select Top 3	Total responses	174	
	Unique participants	59	
	Response options	Count	Percent
	Walking	37	21.26
	Participating in sports, exercise, or physical activities	21	12.07
	Going out, socializing, traveling	20	11.49
	Communication	17	9.77
	Attending school or working	14	8.05
	Performing household tasks or maintenance	14	8.05
	Driving a motor vehicle or community mobility	13	7.47
	Personal hygiene and grooming (bathing, toileting, dressing)	9	5.17
	Sexual activity	8	4.6
	Reading	7	4.02
	Meal preparation	6	3.45
	Other	4	2.3
	Participating in family or pet care	3	1.72
	Eating	1	0.57

Topic 1, Q4. What worries you most about your condition in the future? Select up to 3.	Total responses	195	
	Unique participants	68	
	Response options	Count	Percent
	Losing independence	34	17.44
	Losing ability to communicate	28	14.36
	Having to move to an assisted living or skilled nursing facility	19	9.74
	Not knowing how the disease will progress	18	9.23
	Becoming a burden to my family	18	9.23
	Losing mobility entirely and being bedbound	16	8.21
	Losing ability to swallow	15	7.69
	Losing the ability to walk unassisted/becoming dependent on a mobility	14	7.18
	Dying prematurely	11	5.64
	Not having the energy to work and live as I want to	7	3.59
	Not knowing if I can support myself/family financially	5	2.56
	Not being able to afford my healthcare	4	2.05
	Not being able to care for my children	4	2.05
	Other	2	1.03

*The response rate data for the polling questions are not considered scientific data but provide a snapshot of who participated in the ELPFDD meeting and are meant to complement the live and pre-recorded comments throughout the meeting.

Appendix 2 continued

	Total responses	105	
	Unique participants	47	
	Response options	Count	Percent
	Dietary and herbal supplements	18	17.14
	Prescription medications for muscular issues (Pregabalin, Baclofen, Ama	17	16.19
	Over the counter medications (acetaminophen, ibuprofen)	15	14.29
	Co-Q-10	14	13.33
	Other medications not named above	13	12.38
	Not currently using any medications or supplements	12	11.43
	Medical or recreational marijuana, cannabidiol (CBD)	6	5.71
Topic 2, Q1. Are you using any of the following to manage SCA/DRPLA symptoms? Select all that apply.	Antiseizure medicines	5	4.76
	Psychotropic medications	3	2.86
	Acetyl-DL Leucine	2	1.9

	Total responses	177	
	Unique participants	55	
	Response options	Count	Percent
	Exercise	44	24.86
	Mobility aids (walker, scooter, wheelchair)	32	18.08
	Physical therapy	28	15.82
	Modified home environment	22	12.43
	Occupational therapy	9	5.08
	Speech therapy	8	4.52
	Counseling/therapy	8	4.52
	Aqua therapy	6	3.39
	Other	6	3.39
Topic 2, Q2. Beyond medications and supplements, are you using any of the following to manage SCA/DRPLA symptoms? Select all that apply.	Diet modifications	5	2.82
	Complementary or alternative therapies	3	1.69
	Special education programs	3	1.69
	Not currently using any	3	1.69

*The response rate data for the polling questions are not considered scientific data but provide a snapshot of who participated in the ELPFDD meeting and are meant to complement the live and pre-recorded comments throughout the meeting.

Appendix 2 continued

Topic 2, Q3. How well does your current regimen control your symptoms overall?	Total responses	65	
	Unique participants	65	
	Response options	Count	Percent
	Somewhat	33	50.77
	Very little	19	29.23
	To a great extent	7	10.77
	Not at all	3	4.62
	Not applicable as I am not using any treatments	3	4.62

Topic 2, Q4. What are the major challenges with your current treatment approaches? Select up to 3.	Total responses	129	
	Unique participants	59	
	Response options	Count	Percent
	Not very effective	30	23.26
	High cost or co-pay, not covered by insurance	18	13.95
	Limited availability	17	13.18
	Not applicable as I am not using any treatments	14	10.85
	Negative side effects	12	9.3
	Requires too much of a time commitment	11	8.53
	Requires too much effort	9	6.98
	Other	8	6.2
	Unable to access the services because of transportation issues	5	3.88
	Number of pills/medications needed per day	5	3.88

Topic 2, Q5. Short of a cure, what outcomes are most meaningful to you in a future treatment? Select up to 3.	Total responses	202	
	Unique participants	68	
	Response options	Count	Percent
	Slowing or stopping disease progression	62	30.69
	Improving coordination and balance	51	25.25
	Improving speech	28	13.86
	Improving ability to walk	24	11.88
	Regaining strength and/or muscle function	13	6.44
	Lessening of fatigue	9	4.46
	Improving cognition	4	1.98
	Lessening of pain	3	1.49
	Other	3	1.49
	Capacity to go to school/work	2	0.99
	Decreasing numbness or tingling	2	0.99
	Decreasing seizures	1	0.5

*The response rate data for the polling questions are not considered scientific data but provide a snapshot of who participated in the ELPFDD meeting and are meant to complement the live and pre-recorded comments throughout the meeting.

Appendix 3: Polling Responses Categorized by Disease Subtype

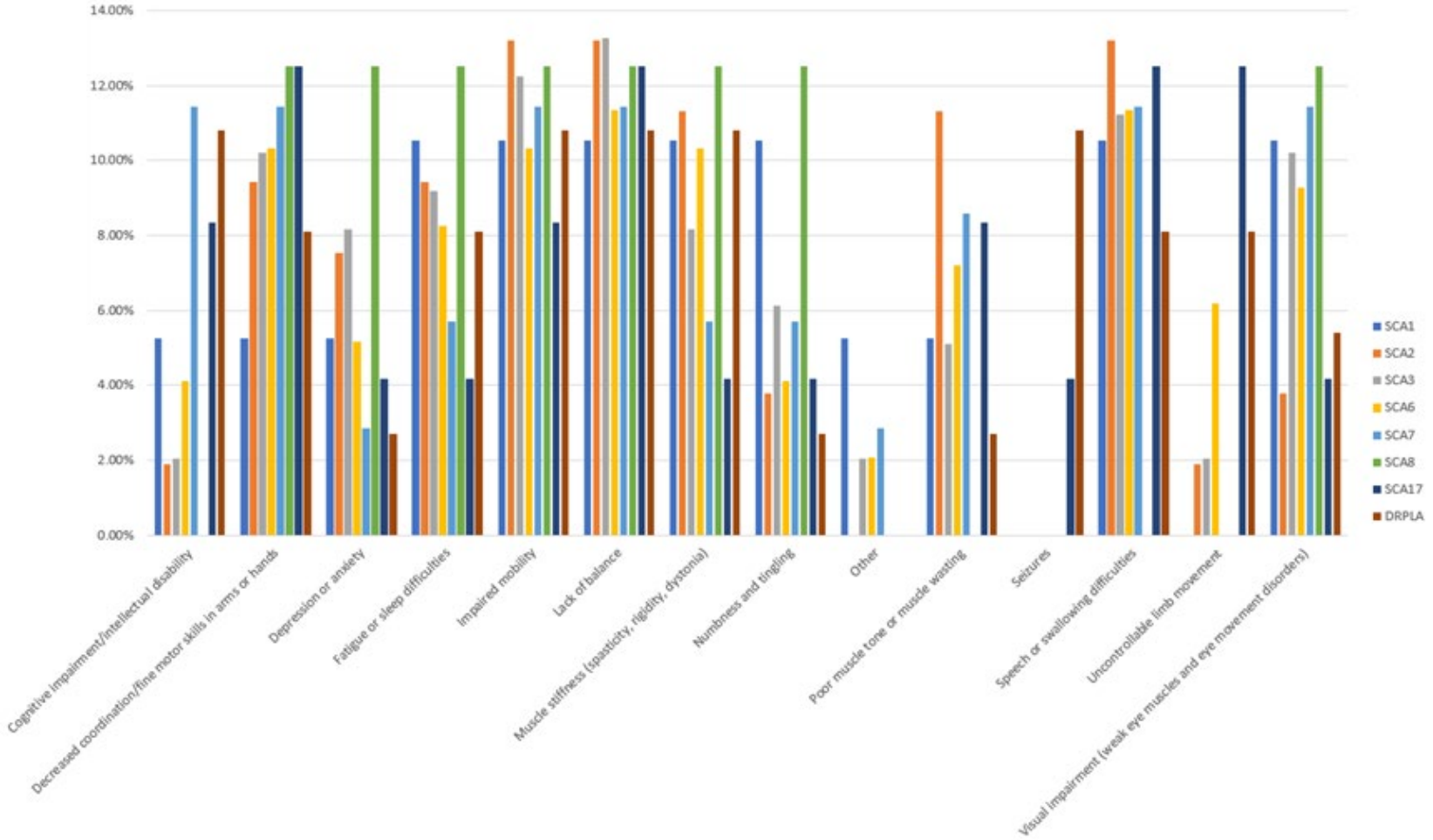
Topic 1, Q1. Which of the following SCA/DRPLA-related health effects does the affected individual have or had in the past? Select ALL that apply									
Responses	**SCA1**	**SCA2**	**SCA3**	**SCA6**	**SCA7**	**SCA8**	**SCA17**	**DRPLA**	**Grand Total**
Cognitive impairment/intellectual disability	5.26%	1.89%	2.04%	4.12%	11.43%	0.00%	8.33%	10.81%	4.85%
Decreased coordination/fine motor skills in arms or hands	5.26%	9.43%	10.20%	10.31%	11.43%	12.50%	12.50%	8.11%	9.97%
Depression or anxiety	5.26%	7.55%	8.16%	5.15%	2.86%	12.50%	4.17%	2.70%	5.93%
Fatigue or sleep difficulties	10.53%	9.43%	9.18%	8.25%	5.71%	12.50%	4.17%	8.11%	8.36%
Impaired mobility	10.53%	13.21%	12.24%	10.31%	11.43%	12.50%	8.33%	10.81%	11.32%
Lack of balance	10.53%	13.21%	13.27%	11.34%	11.43%	12.50%	12.50%	10.81%	12.13%
Muscle stiffness (spasticity, rigidity, dystonia)	10.53%	11.32%	8.16%	10.31%	5.71%	12.50%	4.17%	10.81%	9.16%
Numbness and tingling	10.53%	3.77%	6.12%	4.12%	5.71%	12.50%	4.17%	2.70%	5.12%
Other	5.26%	0.00%	2.04%	2.06%	2.86%	0.00%	0.00%	0.00%	1.62%
Poor muscle tone or muscle wasting	5.26%	11.32%	5.10%	7.22%	8.57%	0.00%	8.33%	2.70%	6.74%
Seizures	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	4.17%	10.81%	1.35%
Speech or swallowing difficulties	10.53%	13.21%	11.22%	11.34%	11.43%	0.00%	12.50%	8.11%	11.05%
Uncontrollable limb movement	0.00%	1.89%	2.04%	6.19%	0.00%	0.00%	12.50%	8.11%	4.04%
Visual impairment (weak eye muscles and eye movement disorders)	10.53%	3.77%	10.20%	9.28%	11.43%	12.50%	4.17%	5.41%	8.36%
Grand Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Topic 1 Q2. Select the most troublesome SCA/DRPLA-related health effects that the affected individual has: Select Top 3									
Responses	**SCA1**	**SCA2**	**SCA3**	**SCA6**	**SCA7**	**SCA8**	**SCA17**	**DRPLA**	**Grand Total**
Cognitive impairment/intellectual disability	11.11%	0.00%	0.00%	3.13%	0.00%	0.00%	8.33%	16.67%	4.20%
Decreased coordination/fine motor skills in arms or hands	0.00%	5.56%	5.13%	12.50%	33.33%	0.00%	16.67%	5.56%	9.79%
Fatigue or sleep difficulties	11.11%	16.67%	15.38%	0.00%	8.33%	0.00%	0.00%	0.00%	7.69%
Impaired mobility	11.11%	27.78%	17.95%	25.00%	8.33%	33.33%	25.00%	11.11%	19.58%
Lack of balance	22.22%	22.22%	28.21%	25.00%	33.33%	33.33%	16.67%	16.67%	24.48%
Muscle stiffness (spasticity, rigidity, dystonia)	0.00%	0.00%	5.13%	9.38%	0.00%	33.33%	8.33%	5.56%	5.59%
Numbness and tingling	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	5.56%	0.70%
Other	11.11%	0.00%	2.56%	3.13%	0.00%	0.00%	0.00%	0.00%	2.10%
Poor muscle tone or muscle wasting	11.11%	0.00%	0.00%	3.13%	0.00%	0.00%	8.33%	0.00%	2.10%
Seizures	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	8.33%	16.67%	2.80%
Speech or swallowing difficulties	22.22%	16.67%	17.95%	18.75%	0.00%	0.00%	8.33%	16.67%	15.38%
Uncontrollable limb movement	0.00%	5.56%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.70%
Visual impairment (weak eye muscles and eye movement disorders)	0.00%	5.56%	7.69%	0.00%	16.67%	0.00%	0.00%	5.56%	4.90%
Grand Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Note: there is variation between the percentage indicated in the cumulative polling data (Appendix 2) and the grand total percentage indicated in Appendix 3. This is because not all participants shared their SCA type and therefore the total number of responses (and percentages) varied slightly when analyzed by SCA type.

Appendix 3 continued: **Topic 1, Q1**

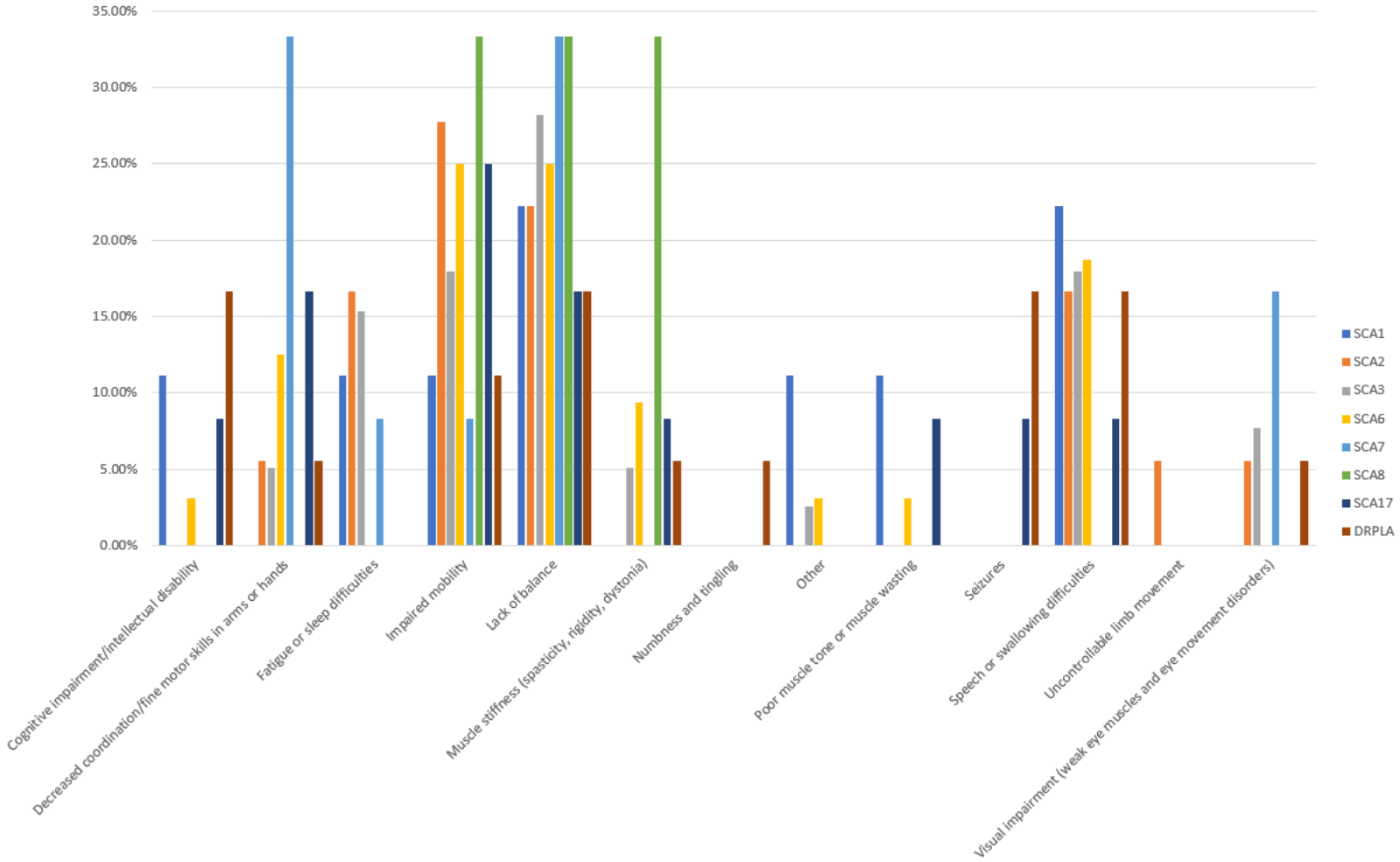
Which of the following SCA/DRPLA-related health effects does the affected individual have or had in the past? Select ALL that apply.



Note: there is variation between the percentage indicated in the cumulative polling data (Appendix 2) and the grand total percentage indicated in Appendix 3. This is because not all participants shared their SCA type and therefore the total number of responses (and percentages) varied slightly when analyzed by SCA type.

Appendix 3 continued: **Topic 1 Q2**

Select the most troublesome SCA/DRPLA-related health effects that the affected individual has. Select top 3.



Note: there is variation between the percentage indicated in the cumulative polling data (Appendix 2) and the grand total percentage indicated in Appendix 3. This is because not all participants shared their SCA type and therefore the total number of responses (and percentages) varied slightly when analyzed by SCA type.

Appendix 3 continued: **Topic 1, Q3 & 4**

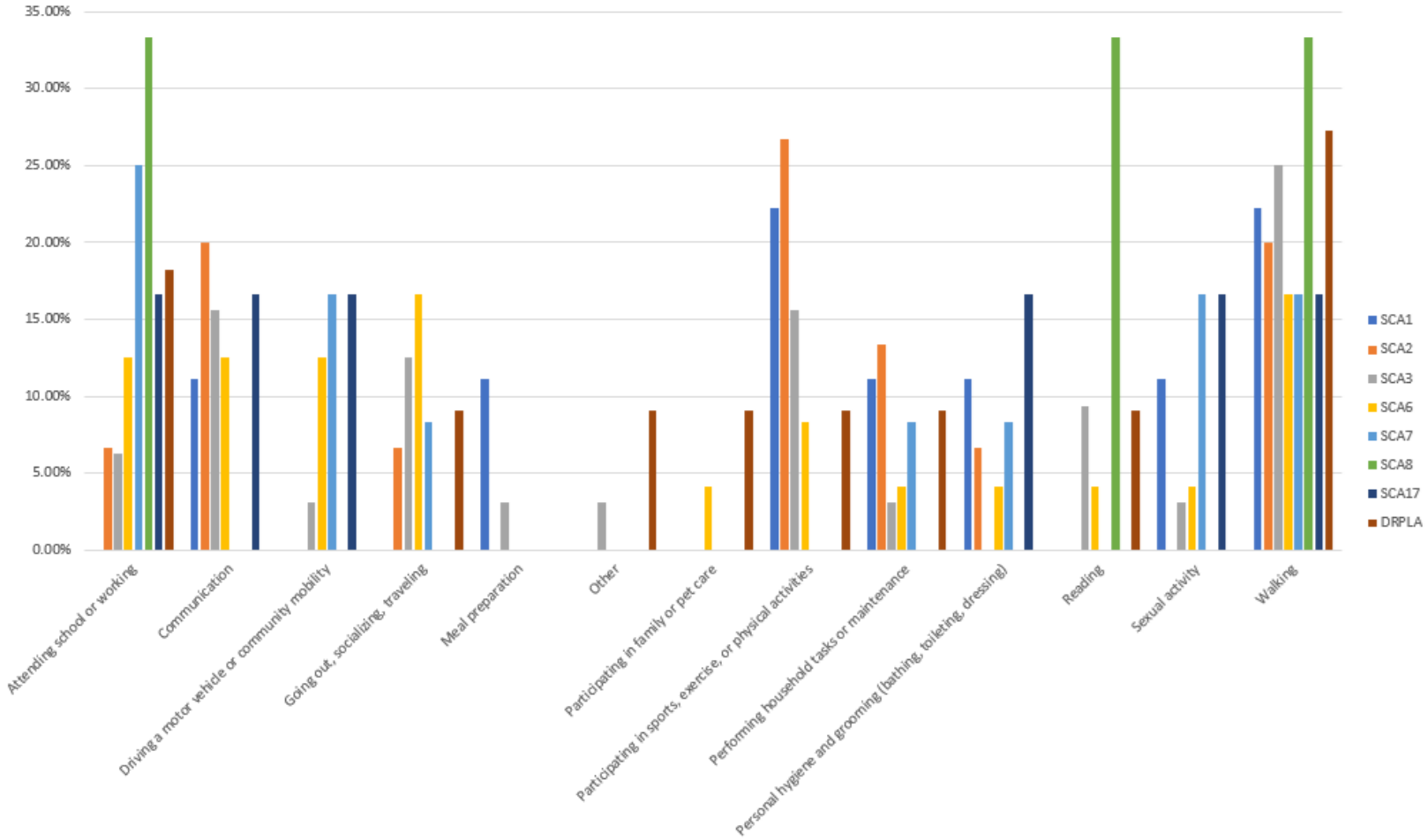
Topic 1, Q3. What specific activities of daily life are most important to you that you are unable or have difficulty doing because of SCA/DRPLA? Select Top 3									
Responses	SCA1	SCA2	SCA3	SCA6	SCA7	SCA8	SCA17	DRPLA	Grand Total
Attending school or working	0.00%	6.67%	6.25%	12.50%	25.00%	33.33%	16.67%	18.18%	11.61%
Communication	11.11%	20.00%	15.63%	12.50%	0.00%	0.00%	16.67%	0.00%	11.61%
Driving a motor vehicle or community mobility	0.00%	0.00%	3.13%	12.50%	16.67%	0.00%	16.67%	0.00%	6.25%
Going out, socializing, traveling	0.00%	6.67%	12.50%	16.67%	8.33%	0.00%	0.00%	9.09%	9.82%
Meal preparation	11.11%	0.00%	3.13%	0.00%	0.00%	0.00%	0.00%	0.00%	1.79%
Other	0.00%	0.00%	3.13%	0.00%	0.00%	0.00%	0.00%	9.09%	1.79%
Participating in family or pet care	0.00%	0.00%	0.00%	4.17%	0.00%	0.00%	0.00%	9.09%	1.79%
Participating in sports, exercise, or physical activities	22.22%	26.67%	15.63%	8.33%	0.00%	0.00%	0.00%	9.09%	12.50%
Performing household tasks or maintenance	11.11%	13.33%	3.13%	4.17%	8.33%	0.00%	0.00%	9.09%	6.25%
Personal hygiene and grooming (bathing, toileting, dressing)	11.11%	6.67%	0.00%	4.17%	8.33%	0.00%	16.67%	0.00%	4.46%
Reading	0.00%	0.00%	9.38%	4.17%	0.00%	33.33%	0.00%	9.09%	5.36%
Sexual activity	11.11%	0.00%	3.13%	4.17%	16.67%	0.00%	16.67%	0.00%	5.36%
Walking	22.22%	20.00%	25.00%	16.67%	16.67%	33.33%	16.67%	27.27%	21.43%
Grand Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Topic 1, Q4. What worries you most about your condition in the future? Select up to 3.									
Responses	SCA1	SCA2	SCA3	SCA6	SCA7	SCA8	SCA17	DRPLA	Grand Total
Becoming a burden to my family	0.00%	13.33%	10.00%	16.67%	0.00%	0.00%	0.00%	0.00%	8.40%
Dying prematurely	16.67%	0.00%	3.33%	3.33%	0.00%	33.33%	16.67%	17.65%	6.72%
Having to move to an assisted living or skilled nursing facility	0.00%	20.00%	3.33%	13.33%	8.33%	0.00%	33.33%	5.88%	10.08%
Losing ability to communicate	0.00%	13.33%	23.33%	10.00%	25.00%	0.00%	0.00%	17.65%	15.13%
Losing ability to swallow	16.67%	6.67%	6.67%	6.67%	16.67%	0.00%	16.67%	17.65%	10.08%
Losing independence	0.00%	13.33%	16.67%	16.67%	33.33%	0.00%	0.00%	11.76%	15.13%
Losing mobility entirely and being bedbound	33.33%	6.67%	6.67%	6.67%	0.00%	0.00%	16.67%	5.88%	7.56%
Losing the ability to walk unassisted/becoming dependent on a mobility device	0.00%	13.33%	10.00%	10.00%	8.33%	0.00%	0.00%	5.88%	8.40%
Not being able to afford my healthcare	0.00%	0.00%	0.00%	3.33%	0.00%	33.33%	0.00%	0.00%	1.68%
Not being able to care for my children	0.00%	6.67%	3.33%	3.33%	0.00%	0.00%	0.00%	0.00%	2.52%
Not having the energy to work and live as I want to	0.00%	6.67%	3.33%	3.33%	0.00%	0.00%	0.00%	5.88%	3.36%
Not knowing how the disease will progress	16.67%	0.00%	10.00%	3.33%	0.00%	33.33%	16.67%	11.76%	7.56%
Not knowing if I can support myself/family financially	16.67%	0.00%	3.33%	3.33%	0.00%	0.00%	0.00%	0.00%	2.52%
Other	0.00%	0.00%	0.00%	0.00%	8.33%	0.00%	0.00%	0.00%	0.84%
Grand Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Note: there is variation between the percentage indicated in the cumulative polling data (Appendix 2) and the grand total percentage indicated in Appendix 3. This is because not all participants shared their SCA type and therefore the total number of responses (and percentages) varied slightly when analyzed by SCA type.

Appendix 3 continued: **Topic 1, Q3**

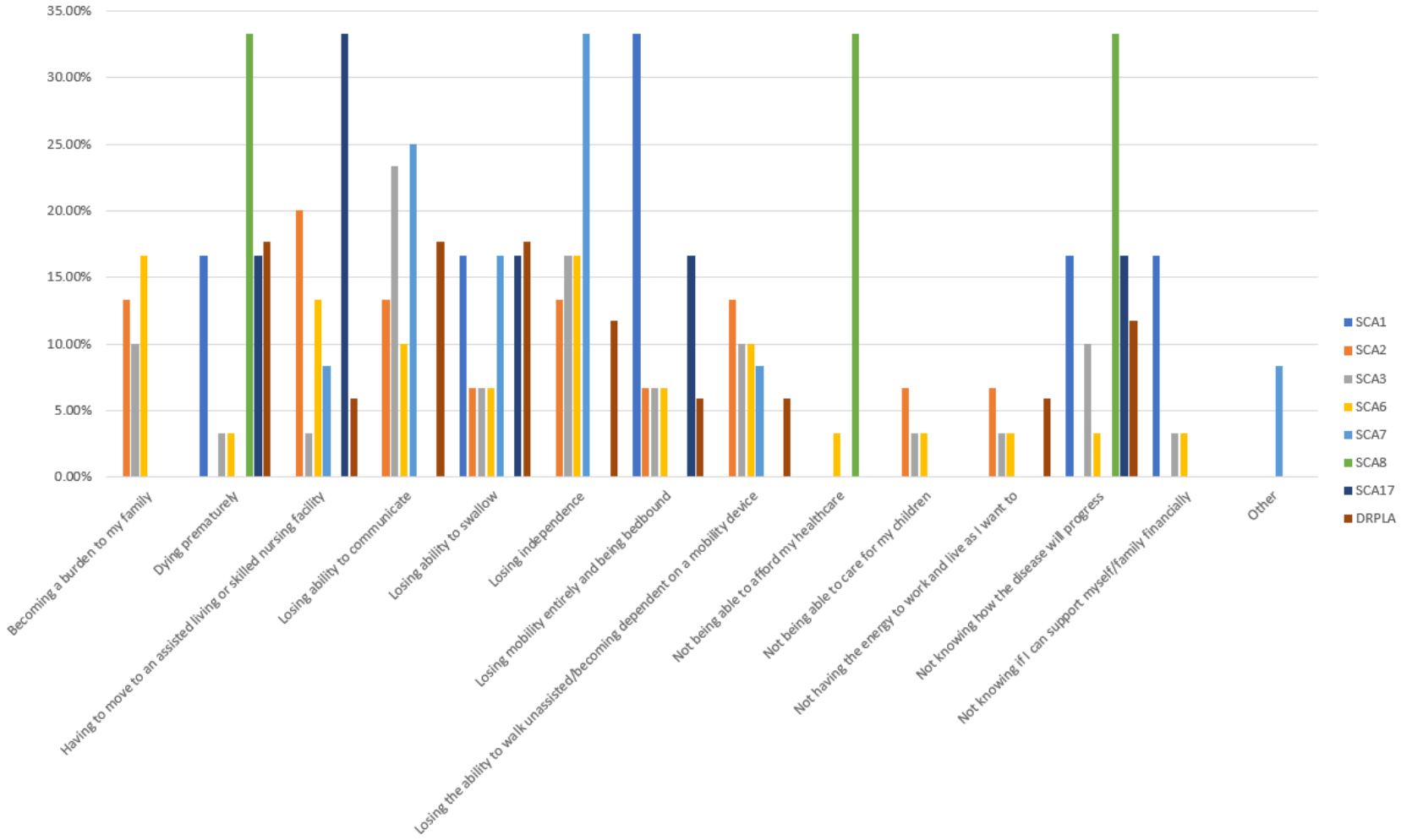
What specific activities of daily life are most important to you that you are unable or have difficulty doing because of SCA/DRPLA? Select top 3.



Note: there is variation between the percentage indicated in the cumulative polling data (Appendix 2) and the grand total percentage indicated in Appendix 3. This is because not all participants shared their SCA type and therefore the total number of responses (and percentages) varied slightly when analyzed by SCA type.

Appendix 3 continued: **Topic 1, Q4**

What worries you most about your condition in the future? Select up to 3.



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Appendix 3 continued: Topic 2, Q1 & 2

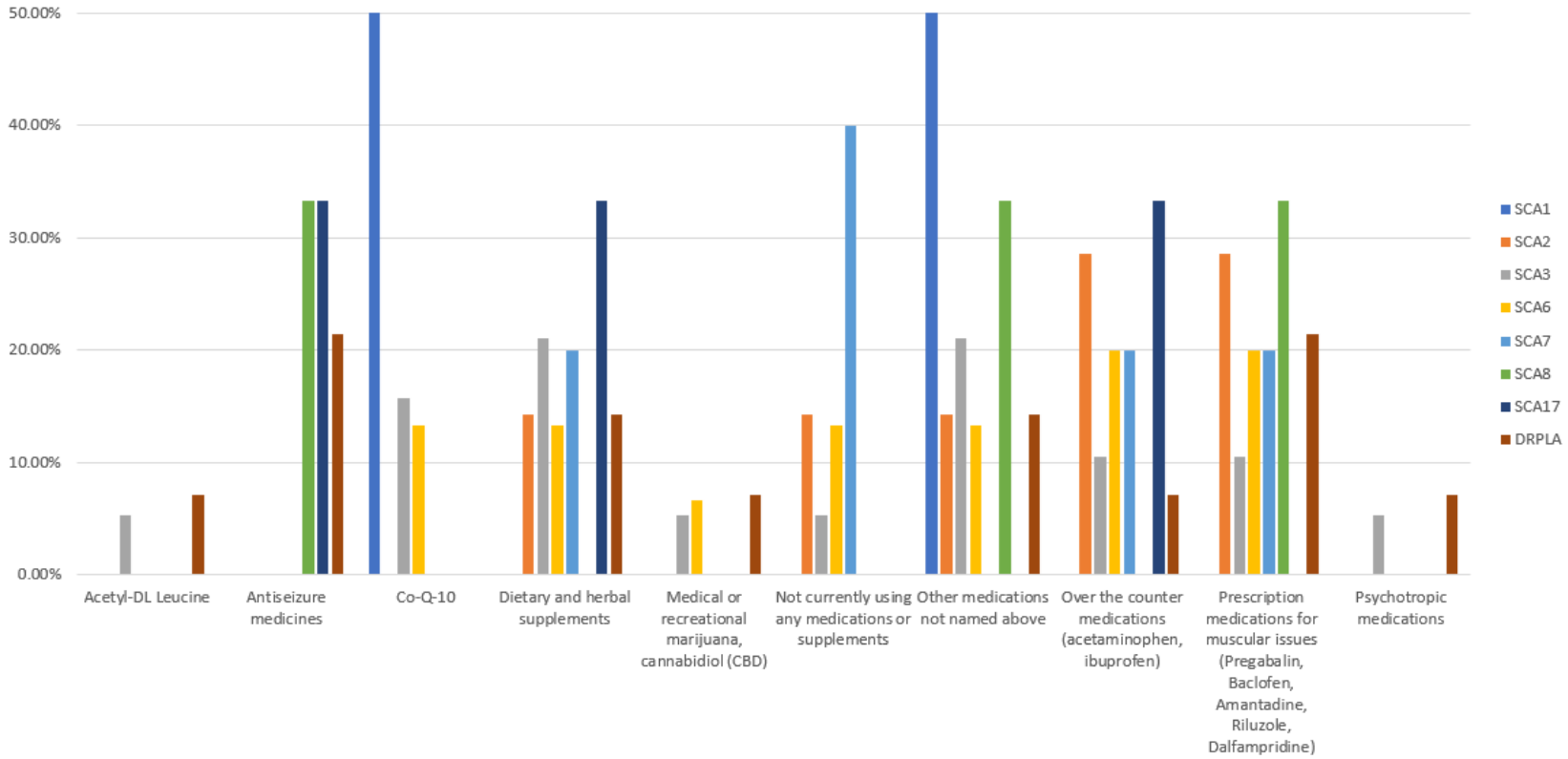
Topic 2, Q1. Are you using any of the following to manage SCA/DRPLA symptoms? Select all that apply.									
Responses	SCA1	SCA2	SCA3	SCA6	SCA7	SCA8	SCA17	DRPLA	Grand Total
Acetyl-DL Leucine	0.00%	0.00%	5.26%	0.00%	0.00%	0.00%	0.00%	7.14%	2.94%
Antiseizure medicines	0.00%	0.00%	0.00%	0.00%	0.00%	33.33%	33.33%	21.43%	7.35%
Co-Q-10	50.00%	0.00%	15.79%	13.33%	0.00%	0.00%	0.00%	0.00%	8.82%
Dietary and herbal supplements	0.00%	14.29%	21.05%	13.33%	20.00%	0.00%	33.33%	14.29%	16.18%
Medical or recreational marijuana, cannabidiol (CBD)	0.00%	0.00%	5.26%	6.67%	0.00%	0.00%	0.00%	7.14%	4.41%
Not currently using any medications or supplements	0.00%	14.29%	5.26%	13.33%	40.00%	0.00%	0.00%	0.00%	8.82%
Other medications not named above	50.00%	14.29%	21.05%	13.33%	0.00%	33.33%	0.00%	14.29%	16.18%
Over the counter medications (acetaminophen, ibuprofen)	0.00%	28.57%	10.53%	20.00%	20.00%	0.00%	33.33%	7.14%	14.71%
Prescription medications for muscular issues (Pregabalin, Baclofen, Amantadine, Riluzole, Dalfampridine)	0.00%	28.57%	10.53%	20.00%	20.00%	33.33%	0.00%	21.43%	17.65%
Psychotropic medications	0.00%	0.00%	5.26%	0.00%	0.00%	0.00%	0.00%	7.14%	2.94%
Grand Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Topic 2, Q2. Beyond medications and supplements, are you using any of the following to manage SCA/DRPLA symptoms? Select all that apply.									
Responses	SCA1	SCA2	SCA3	SCA6	SCA7	SCA8	SCA17	DRPLA	Grand Total
Aqua therapy	0.00%	0.00%	0.00%	5.56%	0.00%	0.00%	0.00%	11.76%	3.33%
Complementary or alternative therapies	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	5.88%	1.11%
Counseling/therapy	0.00%	8.33%	10.53%	0.00%	0.00%	33.33%	0.00%	0.00%	4.44%
Diet modifications	0.00%	0.00%	0.00%	11.11%	0.00%	0.00%	0.00%	0.00%	2.22%
Exercise	33.33%	33.33%	36.84%	22.22%	25.00%	33.33%	16.67%	11.76%	25.56%
Mobility aids (walker, scooter, wheelchair)	33.33%	8.33%	21.05%	16.67%	16.67%	0.00%	0.00%	11.76%	14.44%
Modified home environment	0.00%	16.67%	10.53%	16.67%	16.67%	0.00%	16.67%	11.76%	13.33%
Not currently using any	0.00%	0.00%	5.26%	11.11%	0.00%	0.00%	0.00%	0.00%	3.33%
Occupational therapy	0.00%	0.00%	0.00%	5.56%	16.67%	0.00%	0.00%	5.88%	4.44%
Other	0.00%	8.33%	5.26%	5.56%	0.00%	0.00%	16.67%	0.00%	4.44%
Physical therapy	33.33%	16.67%	10.53%	5.56%	25.00%	33.33%	33.33%	23.53%	17.78%
Special education programs	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	11.76%	2.22%
Speech therapy	0.00%	8.33%	0.00%	0.00%	0.00%	0.00%	16.67%	5.88%	3.33%
Grand Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Note: there is variation between the percentage indicated in the cumulative polling data (Appendix 2) and the grand total percentage indicated in Appendix 3. This is because not all participants shared their SCA type and therefore the total number of responses (and percentages) varied slightly when analyzed by SCA type.

Appendix 3 continued: **Topic 2, Q1**

Are you using any of the following to manage SCA/DRPLA symptoms? Select all that apply.



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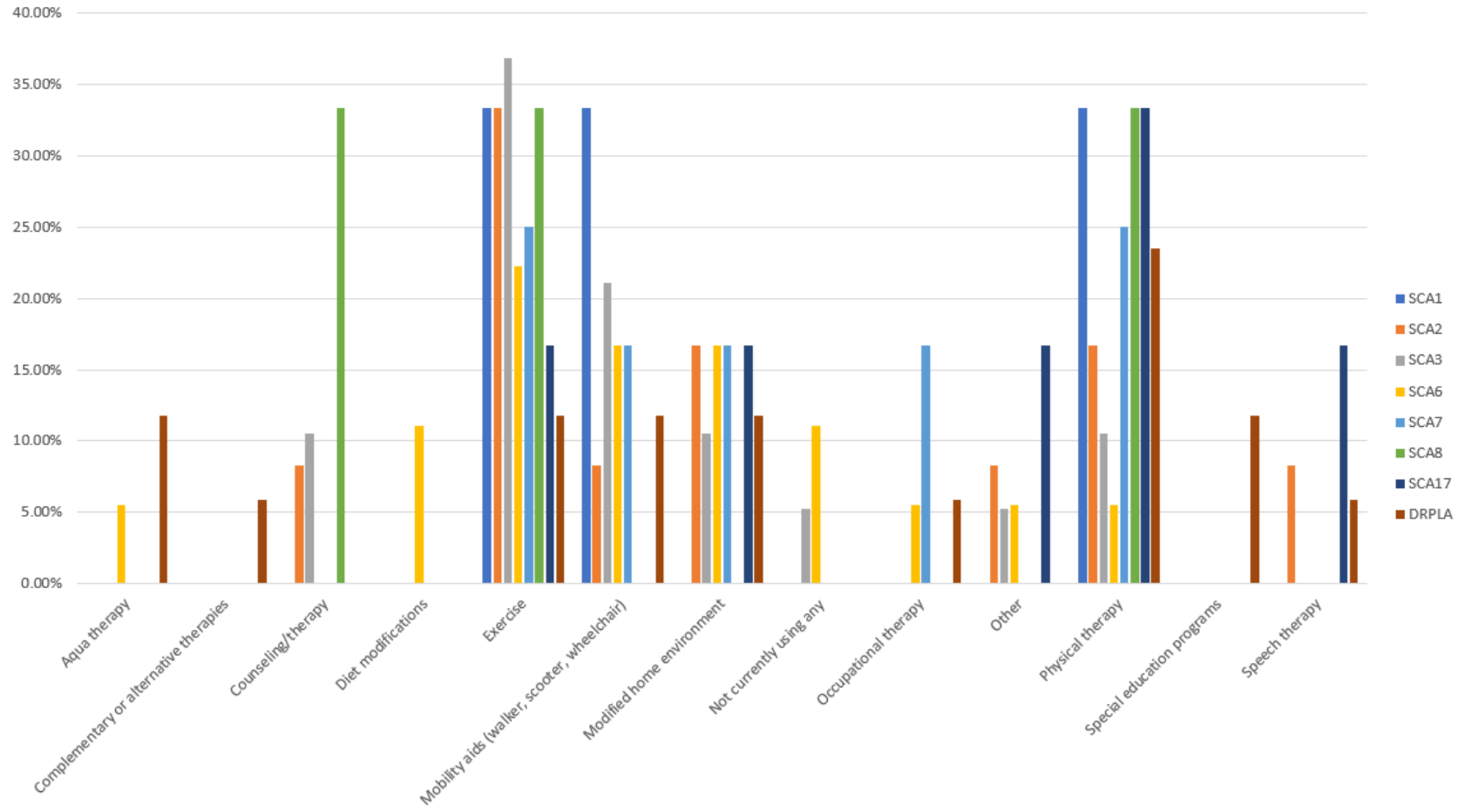
Appendix 3 continued: **Topic 2, Q2**

Beyond medications and supplements, are you using any of the following to manage SCA/DRPLA symptoms? Select all that apply.



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Appendix 3 continued: Topic 3, Q3, 4 & 5

Topic 2, Q3. How well does your current regimen control your symptoms overall?									
Row Labels	**SCA1**	**SCA2**	**SCA3**	**SCA6**	**SCA7**	**SCA8**	**SCA17**	**DRPLA**	**Grand Total**
Not applicable as I am not using any treatments	0.00%	0.00%	0.00%	12.50%	0.00%	0.00%	0.00%	0.00%	3.03%
Not at all	0.00%	0.00%	11.11%	12.50%	0.00%	0.00%	0.00%	25.00%	9.09%
Somewhat	50.00%	50.00%	66.67%	37.50%	33.33%	100.00%	50.00%	25.00%	48.48%
To a great extent	0.00%	25.00%	0.00%	12.50%	66.67%	0.00%	0.00%	0.00%	12.12%
Very little	50.00%	25.00%	22.22%	25.00%	0.00%	0.00%	50.00%	50.00%	27.27%
Grand Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Topic 2, Q4. What are the major challenges with your current treatment approaches? Select up to 3.									
Responses	**SCA1**	**SCA2**	**SCA3**	**SCA6**	**SCA7**	**SCA8**	**SCA17**	**DRPLA**	**Grand Total**
High cost or co-pay, not covered by insurance	16.67%	8.33%	11.76%	16.67%	16.67%	33.33%	25.00%	12.50%	14.86%
Limited availability	0.00%	8.33%	5.88%	22.22%	0.00%	33.33%	0.00%	12.50%	10.81%
Negative side effects	16.67%	8.33%	5.88%	5.56%	16.67%	0.00%	25.00%	12.50%	9.46%
Not applicable as I am not using any treatments	0.00%	8.33%	11.76%	16.67%	0.00%	0.00%	0.00%	0.00%	8.11%
Not very effective	50.00%	16.67%	29.41%	27.78%	0.00%	0.00%	25.00%	37.50%	25.68%
Number of pills/medications needed per day	0.00%	8.33%	0.00%	0.00%	0.00%	0.00%	0.00%	25.00%	4.05%
Other	16.67%	0.00%	5.88%	5.56%	0.00%	0.00%	25.00%	0.00%	5.41%
Requires too much effort	0.00%	16.67%	11.76%	0.00%	33.33%	0.00%	0.00%	0.00%	8.11%
Requires too much of a time commitment	0.00%	25.00%	17.65%	0.00%	33.33%	33.33%	0.00%	0.00%	12.16%
Unable to access the services because of transportation issues	0.00%	0.00%	0.00%	5.56%	0.00%	0.00%	0.00%	0.00%	1.35%
Grand Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Topic 2, Q5. Short of a cure, what outcomes are most meaningful to you in a future treatment? Select up to 3.									
Response	**SCA1**	**SCA2**	**SCA3**	**SCA6**	**SCA7**	**SCA8**	**SCA17**	**DRPLA**	**Grand Total**
Capacity to go to school/work	11.11%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	1.01%
Decreasing numbness or tingling	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	8.33%	1.01%
Decreasing seizures	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	8.33%	1.01%
Improving ability to walk	11.11%	25.00%	14.29%	4.17%	11.11%	33.33%	11.11%	8.33%	12.12%
Improving cognition	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	11.11%	0.00%	1.01%
Improving coordination and balance	22.22%	33.33%	28.57%	25.00%	33.33%	0.00%	22.22%	8.33%	24.24%
Improving speech	11.11%	0.00%	14.29%	16.67%	22.22%	0.00%	11.11%	8.33%	12.12%
Lessening of fatigue	0.00%	0.00%	4.76%	0.00%	0.00%	33.33%	0.00%	8.33%	3.03%
Lessening of pain	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	8.33%	1.01%
Other	11.11%	0.00%	0.00%	4.17%	0.00%	0.00%	0.00%	0.00%	2.02%
Regaining strength and/or muscle function	0.00%	8.33%	9.52%	16.67%	0.00%	0.00%	11.11%	8.33%	9.09%
Slowing or stopping disease progression	33.33%	33.33%	28.57%	33.33%	33.33%	33.33%	33.33%	33.33%	32.32%
Grand Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

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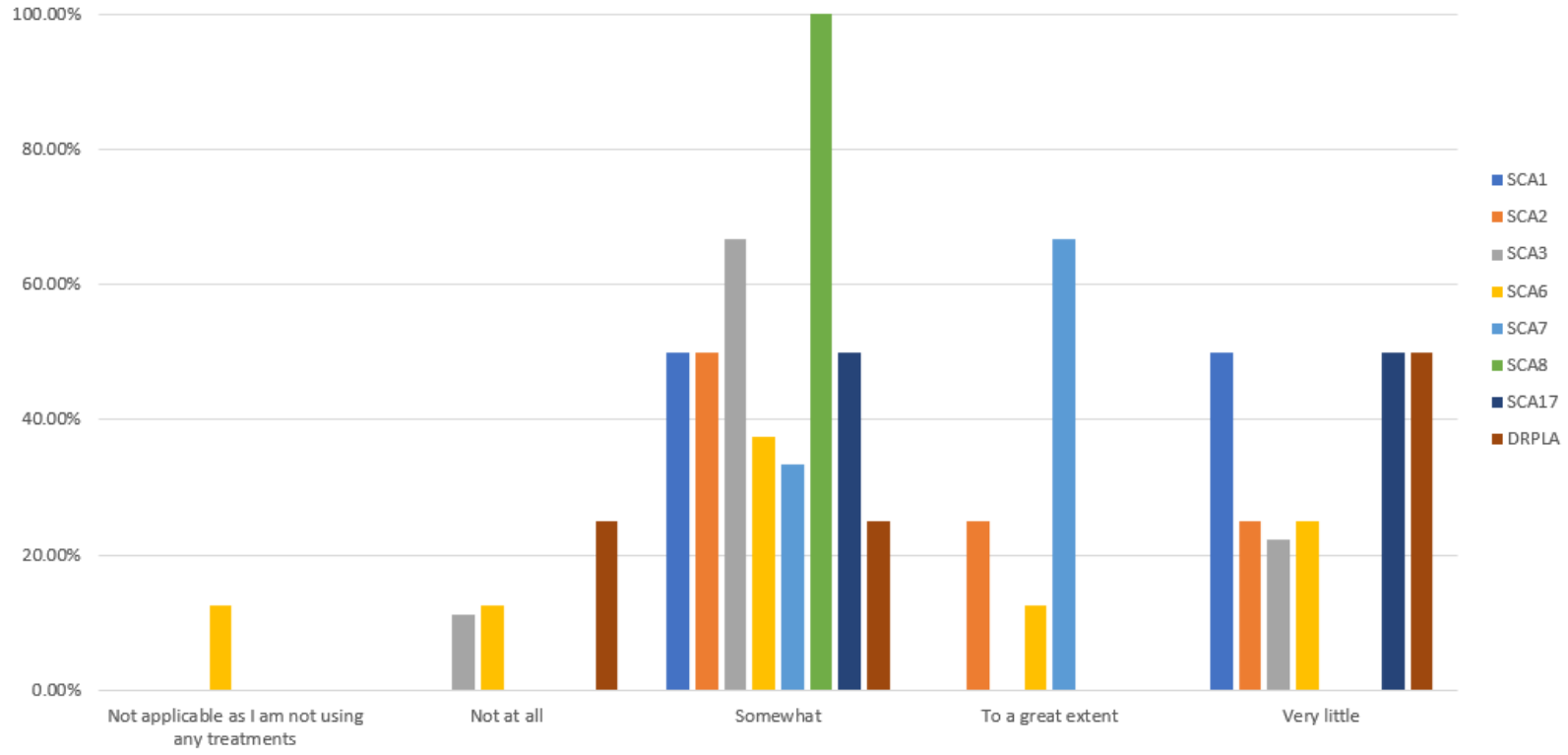
Appendix 3 continued: **Topic 2, Q3**

How well does your current regimen control your symptoms overall?



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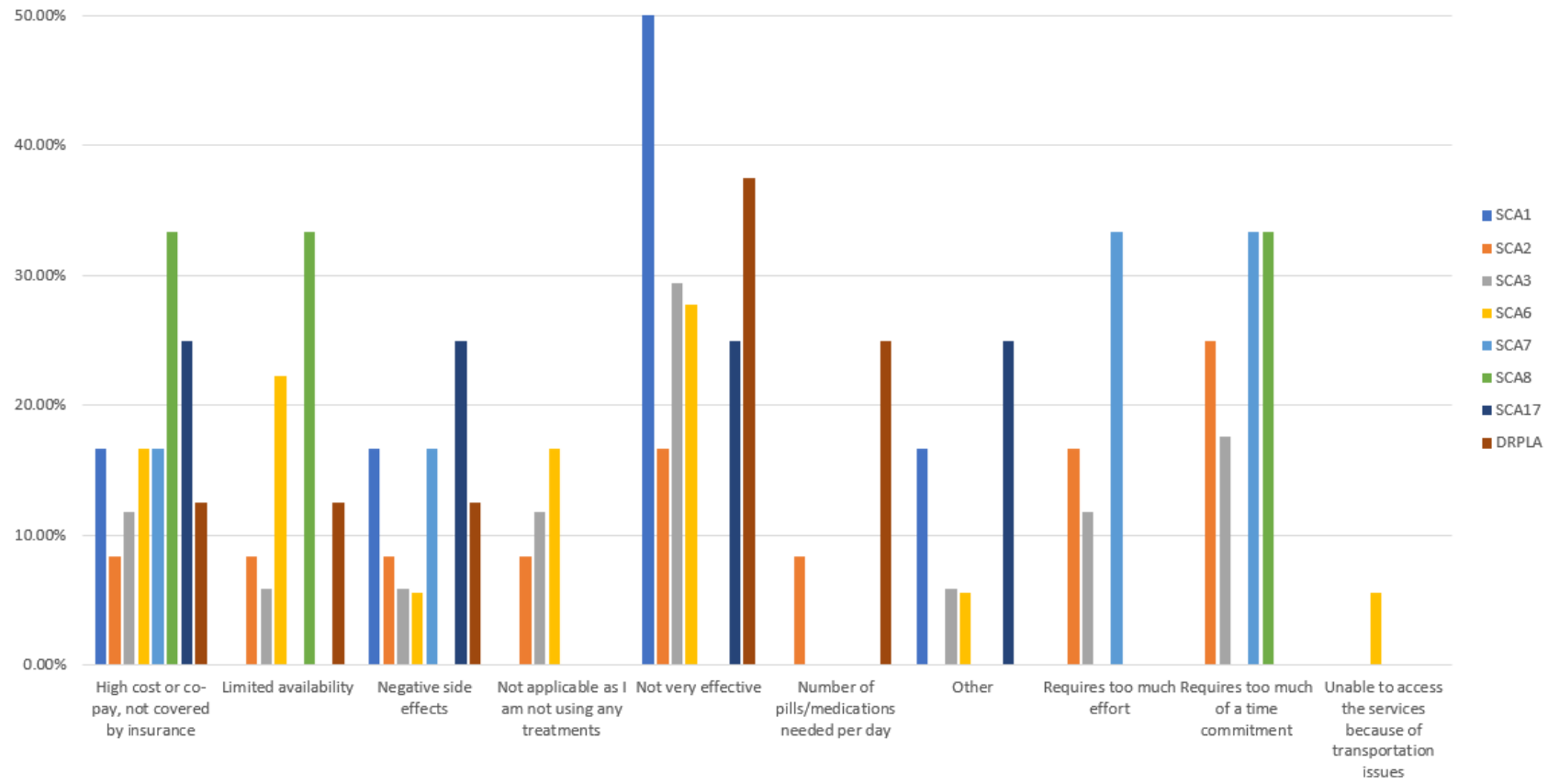
Appendix 3 continued: **Topic 2, Q4**

What are the major challenges with your current treatment approaches? Select up to 3.



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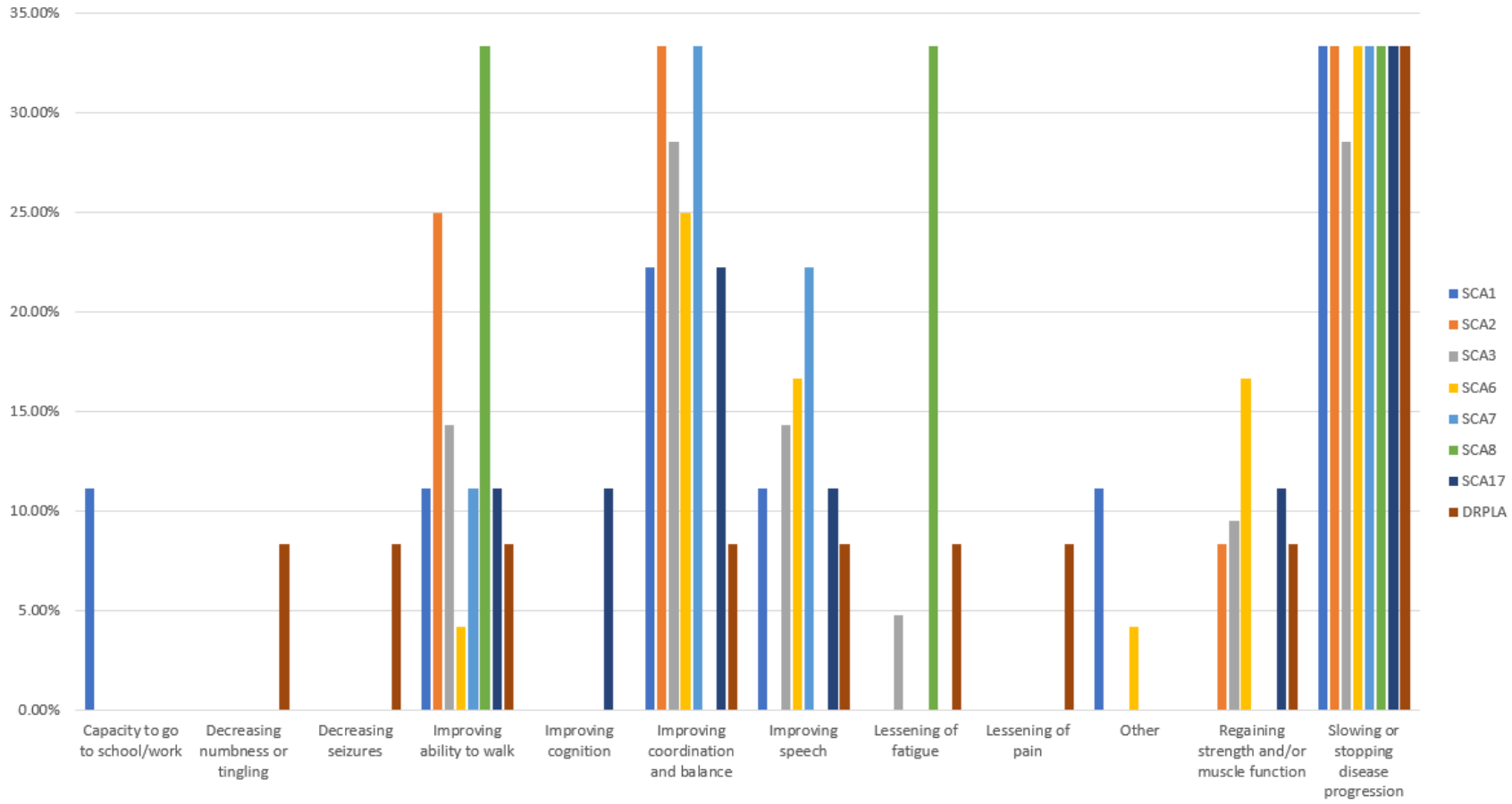
Appendix 3 continued: **Topic 2, Q5**

Short of a cure, what outcomes are most meaningful to you in a future treatment? Select up to 3.



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Appendix 4: Discussion Questions

TOPIC 1 – LIVING WITH SCA/DRPLA: SYMPTOMS AND DAILY IMPACT

1. For the person who is affected with SCA/DRPLA, please identify 1-3 symptoms that have the most significant impact.

a) Currently which symptoms most affect the person with SCA/DRPLA?
b) Which symptoms were the most significant at other times for the person with SCA/DRPLA?
c) When looking back after being diagnosed with SCA/DRPLA what were the first symptoms the person with SCA/DRPLA experienced?

2. How have symptoms changed or progressed over time?

3. How does SCA/DRPLA affect the person with SCA/DRPLA on the best days? On the worst days?

4. Are there specific activities that are important to the person with SCA/DRPLA that cannot be done at all or as fully as you would like because of SCA/DRPLA?

a) How does it affect life activities (school/work, abilities, relationships, self-sufficiency, living situation, activities, etc.)?
b) If the person with SCA/DRPLA could do one activity that they currently are unable to, what would it be?

6. What worries you the most as you get older for either yourself or for the person with SCA/DRPLA?

TOPIC 2 – PERSPECTIVE ON CURRENT AND FUTURE APPROACHES TO TREATMENT*

1. What are you currently doing to manage your SCA/DRPLA symptoms?

a) Which specific SCA/DRPLA symptoms do the treatments address?
b) How has this treatment regimen changed over time and why?

2. How effective have these treatments been for you/the affected individual?

a) How well do these treatments improve the ability to do specific activities that are important in daily life?

3. What are the most significant downsides to current treatments and how do they affect daily life?
(Examples of downsides may include bothersome side effects, going to the hospital for treatment, etc.)

4. Short of a complete cure, what specific things would you want for an ideal treatment for SCA/DRPLA? When considering a new treatment, what factors are important to you?

a. What questions/data/information would you want to consider?

b. Imagining that there were multiple treatment options approved, what factors into your decision on which treatment to choose?

Appendix 5: September 25, 2020 Meeting Agenda

9:30-10:00 a.m. **Online Registration**: https://ataxia.org/el-pfdd-meeting/

10:00-10:05 a.m. **Welcome Remarks** – *NAF Executive Director: Andrew Rosen & Cure DRPLA President & Co-Founder: Andrea Compton*

10:05-10:15 a.m. **FDA Opening Remarks** –*Dr. Wilson W. Bryan, MD* (Deputy Director of Office of Tissues and Advanced Therapies)

10:15-10:30 a.m. **Clinical Features of SCA & Therapeutic Approaches** – *Dr. George Wilmot, MD, PhD, Associate Professor in Movement Disorders at Emory University*

10:30-10:35 a.m. **Meeting Overview**– *James Valentine, Moderator*

10:35-10:40 a.m. **Demographic Polling** – *James Valentine*

10:40 a.m.-11:20 p.m. **Topic 1: Living with SCA /DRPLA** (How do the symptoms and health effects impact patient lives? What most worries patients?)

- Panel 1A *(4 panelists):* Ataxia and other neuromuscular impacts (balance, chorea, spasticity, weakness, reflexes, and gait) (20 mins)
- Panel 1B *(4 panelists):* Other symptoms and health effects (visual problems, speech, swallowing, memory and dementia, epilepsy, behavior issues) (20 mins)

11:20-12:30 p.m.-**Polling & Audience Discussion**

12:30-1:00 p.m.- **Lunch**

1:00-1:05 p.m.- **Featured Video** of Severely Impacted Individual

1:05-1:35 p.m.- **Topic 2*:* Approaches to Treatments for SCA/DRPLA** (What considerations for clinical trials are most important to SCA/DRPLA patients? How do current treatment approaches help and what burdens do they add? What do patients/caregivers want from a future treatment?)

- Panel 2 (30 mins)

1:35-2:45 p.m.- **Polling & Audience Discussion**

2:45-2:50 p.m.- **Summary Remarks** *(Larry Bauer)*

2:50-3:00 p.m.- **Concluding Remarks & Next Steps** – *NAF & CureDRPLA Leadership*

Appendix 6: Patient Panel Participants

Pre-recorded Panel 1A:

- Stephanie W.- Individual affected by SCA6
- Destinee J.- Young Adult affected by SCA2
- Gina L.- Individual affected by SCA3
- Jason and Sherri H.- Jason is affected by SCA7, Sherri is a wife and caregiver. Both of their children and Jason's mother are deceased from SCA7

Pre-recorded Panel 1B:

- Cristi B.- wife, mother and caregiver. Her husband and daughter have DRPLA. Her son Reggie died from DRPLA related complications.
- Cameryn C.- Young Adult affected by SCA7
- Tom S.- Individual affected by SCA1
- Jeannette V.- Individual affected by SCA3

Topic 1 LIVE Discussion Starters:

- Robert S.– 65 year old with adult onset DRPLA
- Devin and Laura C.- Father, mother and caregivers of adult with SCA7
- Dana C.- Individual affected by SCA2
- Paul C.- father and caregiver of a 14 year old with DRPLA
- Jodie K.- Individual affected by SCA2

Featured Video:

- Junko S.- Wife, mother, and caregiver. Her husband passed away from DRPLA. Her daughter lives with DRPLA.

Pre-recorded Panel 2:

- Kerri M.- Mother of 7 children, of which 4 young children live with DRPLA
- Hannah X.- Young mother affected by SCA1
- Jessica O.- Pre-symptomatic individual who lives with anticipated onset of SCA3; father also affected
- Brett M.- Individual affected by SCA1
- Eric P. and Michelle N.- Brother and Sister. Eric lives with SCA2. Michelle is an important part of Eric's support system

Topic 2 LIVE Discussion Starters:

- Maja J.- Wife and mother of husband and son, who both live with DRPLA
- Brian K.- Individual who lives with SCA7
- Doug P.- Individual who lives with SCA6
- Jessica O.- Pre-symptomatic individual who lives with anticipated onset of SCA3; father also affected
- Greg R.- Individual who lives with SCA2